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VOLUME 27 JULY 1960 No. 1

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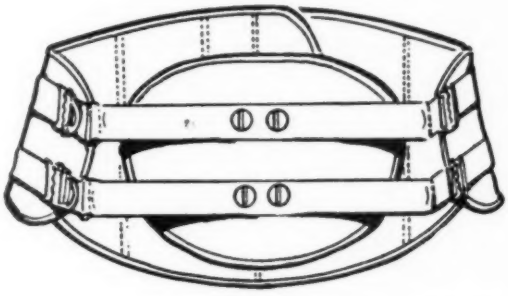

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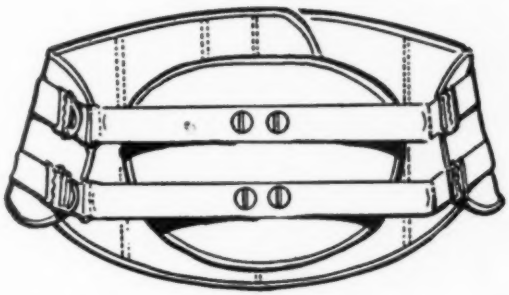

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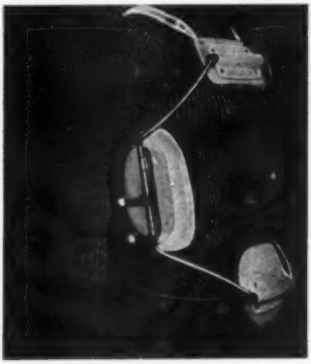

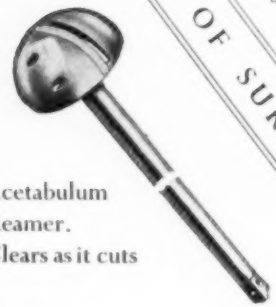

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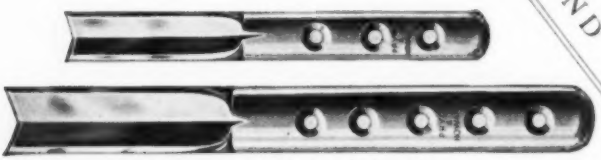

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REFLECTIONS ON SPECIALIZATION IN MEDICINE

The First Watson-Jones Lecture delivered at the Royal College of Surgeons of England

on

9th December 1959

by

The Rt. Hon. Lord Cohen of Birkenhead, M.D., D.Sc., LL.D., F.R.C.P.

EPONYMOUS LECTURES ARE almost without exception a tribute to those who have passed from us. They tend to be memorials in panegyric form to a great figure of the past, and to exemplify the exhortation—*De mortuis nil nisi bonum*. Not infrequently they give support to Dr. Johnson's observation that " in lapidary inscriptions a man is not upon oath ". But to-day the position is different and more difficult.

To-day, he whom we are gathered to honour is vigorously active and at the zenith of his most distinguished career. Therefore, notwithstanding the counsel of Dr. Johnson, who wrote, " You should never speak of a man in his presence, it is always indelicate and it may be offensive," my first words, though brief, must be of Sir Reginald.

We were fellow-students and, for many years, colleagues on the staff of the Liverpool Royal Infirmary, and we have been firm, ardent friends since, a fact which accounts more than any other for my having been invited, and no honour has been more acceptable to me, to deliver the first of the lectures which bear his name. He chose to be a surgeon, but chance determined that his future lay in orthopaedic surgery, then a rapidly developing specialty, to which his dynamic and brilliant personality was to give explosive impetus. In the spirit of Harvey and Hunter he was not prepared to accept the teaching of authority unless the facts so warranted, and thus, within a few years, his penetrating and original observations, clearly and strikingly presented, enriched the literature of his subject. Then twenty years ago appeared the first edition of his *Fractures and Joint Injuries*, which immediately became the classic text. This stamped him the mentor of his generation of orthopaedic surgeons. Like Leonardo da Vinci, he had excelled his masters.

Of his work in war and peace, which has gained for him world-wide renown, admiration and gratitude, and of the honours which have been showered upon him, this is not the moment to speak. But to one aspect of his work I must refer since it provides the *motif* for my lecture. He played the paramount role in the resurgence of rehabilitation as a therapeutic agent. For him " diseases " and " injuries " are but useful and convenient conceptional symbols. What matters to him is to restore a sick and hurt man to his full potentiality of health and activity. He never forgets John Smith or Mary Jones—the *whole* person. He rejects with

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Plato the dichotomy of mind and body. He is, despite his pre-eminence in orthopaedic surgery, first a good doctor, with wide interests in medicine. The foundations of this " holistic " approach to medicine were early laid. The first paper he published, 35 years ago, was on " Tabes dorsalis in surgical practice", and his early papers on calcification of bone gave evidence, not only of his scientific training and background, but also promise of that catholicity of outlook which has characterized his later writings.

It was this facet of Sir Reginald's work which led me to reflect on specialization in medicine, on the paradox that whilst advancing knowledge must inevitably lead to specialization in all fields, yet for the practice of medicine especially, but also for medical teaching and research, is demanded breadth of outlook and a wide range of knowledge. Here lies the conflict and the challenge in an age in which specialization is the endemic disease of medicine. New specialties are arising almost daily. Twenty-five years ago in the U.S.A., when the Advisory Board for Medical Specialties was first established, there were four specialty boards. In 1958, there were eighteen specialty boards issuing certificates in 51 different specialties or sub-specialties of medicine. I have said that specialization is not confined to medicine. It is growing with uncontrollable speed in all branches of knowledge and techniques. The chemistry which our fathers knew became inorganic, physical, and organic, and later not only biochemistry appeared, but specialisms in yet narrower fields—protein chemistry, colloid chemistry, etc., and in special chemical techniques—such as chromatography, spectroscopic analysis, microradiology, isotopes. Yet it would be to fall into a common error to believe with the medical historian, Castiglione, that specialism is of recent origin. Speaking of the 17th century, he writes : " At the end of this century . . . already various specialties began to be detached from the main trunk. Surgery became an art comparable in dignity to medicine. Anatomy, removed from the hands of the barber surgeons, became an exact science on which physicians leaned with respect. Hygiene, sanitation and legal medicine codified their principles; obstetrics, ophthalmology and dentistry became disciplines organized on scientific foundations. . . . Here we have an extensive preparation for modern medicine." This view of the origin of specialties —that they branch off from the corpus of knowledge when it outgrows the capacity of any one man's intellectual embrace—cannot be maintained. If I may adapt Ben Jonson's phrase, " It is not growing like a tree, in bulk doth make a specialty." Specialization has been a continuing component of civilization since its earliest recorded history. And not in medicine only. The tomb of Tutankhamen, when opened, disclosed priceless art treasures which could have been wrought only by specially skilled hands.

Our chief authority for specialization in Egyptian medicine is Junker, whose excavations in 1926 in the old Empire cemetery near the Great

Pyramid of Gizeh brought to light a *stela* with a funereal inscription from the tomb of a court physician of the Sixth Dynasty (about 2600 B.C.) named Pepi-ánkh, who is described as " The physician of the belly of the Pharao, the guardian of the anus, the physician of the eyes, and the surveyor of the physicians." In the 5th century B.C. we find Herodotus in his *Persian Wars* (II. 84) writing of the Egyptians: " The art of medicine is thus divided ; each physician applies himself to one disease only and not more. All places abound in physicians; some are for the eyes, others for the head, others for the teeth, others for the intestines, and others for internal disorders."

These specialists were, according to Diodorus Siculus, employed by the state and all the sick were treated without cost. Physicians were required to use official remedies only. Only if these proved unavailing could they resort to others. But if the death of the patient followed any transgression from written authority the penalty was death! There are some who would have us believe that the National Health Service in this context lends point to George Santayana's aphorism : " He who is disposed to ignore history must be prepared to repeat it."

In the golden age of Greece the prevailing philosophy frowned on specialism : " This is the greatest error in the treatment of sickness," wrote Plato, " that there are physicians for the body and physicians for the soul, and yet the body and soul are one and indivisible." This attitude stems from the abstract nature of Greek thought. For the Greeks, reason was master. Nature might be observed, but disregarded if she contradicted the master, Reason. Pervading the whole of Greek thought was the attempt to conceive nature as a whole without an adequate knowledge of its parts; to generalize from inadequate particulars, to transcend experience by dialectics. In Empedocles we see nature conceived as a whole, derived from the four elements—fire, earth, air and water; even before Aristotle there developed the concept of four associated qualities—heat and cold, dryness and moisture—and of the four humours of the body—blood, phlegm, yellow bile and black bile. Thus Plato, in *Timaeus*, asserted that health was balance and disease imbalance of the four humours.

The humoral theory stamped the seal of " holism " on Greek medicine; it was to dominate medical theory for over two thousand years and its traces are still to be discerned in current nomenclature. Gout and rheumatism derive from the dropping or flow of peccant humours into abnormal sites, and melancholia reflects the ancient doctrine that depression is due to an excess of black bile.

Yet even within the humoral theory were to be found specialisms. For example, the Dogmatists, accepting humoral theory, wove into it the Pythagorean doctrine of numbers, especially 7—second teeth at 7 years, puberty at 14 years, growth of beard at 21 years. Again, the Methodists

thought of man as an infinity of small particles (" atoms ") and pores. If the pores were relaxed, thus presumably facilitating the spread of humours into abnormal sites, the appropriate treatment was astringents—cold baths, vinegar, alum, chalk, lead. If the pores were contracted, preventing the escape of peccant humours, then laxatives, venesection, cupping, leeches, poultices and fomentations were indicated. This dualistic concept of Methodism reached its peak in the 18th century, when John Brown created the most popular system of its day—Brunonism—which affirmed that life is maintained by continuous stimuli producing " excitement " of tissues. Diseases were " sthenic " or " asthenic " depending on whether " excitement " was increased or diminished—a diagnosis which depended chiefly on the pulse and temperature, but also on various other items of the general state of the body. Treatment for the " sthenic " was opium and for the " asthenic " alcohol, which no doubt accounted for the popularity of the system. Brown succumbed to an excess of self-medication!

But to return to the greatest of the Greek physicians, Hippocrates, who nearly 2,400 years ago was writing not only on *Medicine, Prognostics, Epidemic Diseases, Air Waters and Places* (the first work on ecology and climatology), but also on *Fractures, Dislocations and Wounds of the Head.* Here was no specialist, but a man who had thrown off the shackles of pure reason which fettered his medical contemporaries. He observed accurately and without preconceived theory the phenomena of disease, and sought by repeated observation, analogy and extrapolation to anticipate the course of disease. Although he might have rescued medicine from the theories of his philosophically idealist contemporaries, conservatism prevailed and for centuries the unity of medicine as expounded by Hippocrates was lost. Celsus, about the third decade A.D., writes in the introduction to his *De Medicina* that after Hippocrates, the Art of Medicine was divided into three parts—dietetics, pharmaceutics and surgery; he makes reference to specialists, for instance to " Eucepides, the most famous oculist of our time ". The poet Martial, writing towards the end of the 1st century A.D., speaks satirically of some of the popular specialists then practising in Rome: " Cascellius extracts or fills an aching tooth, Hyginus burns away the hairs that hurt the eyes; Fannius relieves, without cutting, the relaxed uvula; Eros effaces the melancholy brand-marks of slavery from freedmen's foreheads; Hermes is a very Podalirius in curing hernia; but tell me, Gallus, where is that that can help my harassed person? "

The centuries passed with but little change in the structure of medicine. In the Middle Ages, in this country as elsewhere, " irregular " healers in very narrow fields, who had existed for centuries, then flourished because of the shortcomings of medicine itself. The victims of eye diseases were ready prey for the itinerant quack. There appeared, for example, in 1694 in the Strand, William Read. He set up as an oculist " having hired

someone to write a book on eye diseases under his name, and a Grub Street poet to praise him in verse". But he was sufficiently impressive to be consulted by Queen Anne, and was later knighted and appointed oculist to George I. In this field practised also Chevalier John Taylor, who travelled around Europe in a coach decorated with painted eyes, and trumpeted his own praises in latinised English, which he described as "true Ciceronian", though Dr. Johnson penetrated his charlatanism and buffoonery in the scathing comment: "Taylor was the most ignorant man I ever knew." Yet some who had received no formal medical training wrote important texts; for instance, *De Oculis* of Benevenutus Crassus of Jerusalem (1474) deals commendably with cataract and ophthalmia (probably trachomatous).

There were also roving dentists, portrayed in market and town-square in many contemporary prints; and the stone-surgeons who by palming pretended to remove stones from the heads of mental defectives. There were herniotomists and lithotomists; but none of the latter could vie in popularity with Joanna Stevens, a widow who sold "a remedy for the stone" to such effect that she succeeded in having the recipe purchased by the Government by Act of Parliament in 1739. Its ingredients—a mixture of eggshells, snails, soap, herbs, etc.—were of no value and in each of her certified "cures" an autopsy revealed the bladder stones.

Modern orthopaedic surgery stems directly from the bone-setter of the middle ages. Hippocrates' *Fractures, Dislocations and Head-wounds* had pointed a way along which Ambroise Paré, Glisson and others were to advance, yet bone-setting was the work of quacks. Some were complete impostors. Such was Mrs. Mapp, yet her practice was so lucrative that she could drive in from Epsom in a chariot and four with ostentatiously liveried servants. Others from country districts, and especially agricultural communities, developed successful techniques which were handed down from parent to child. From such a family of bone-setters in Anglesey came Hugh Owen Thomas, the father of modern orthopaedic surgery, and his nephew, Robert Jones.

By the 2nd century A.D., the time of Galen, physicians who dealt with internal diseases refrained from surgery. Surgery emerged as a separate discipline because physicians forgot Hippocrates. Though blood letting and wound surgery were necessary, the physician would not demean himself by soiling his hands. These were tasks for the surgeon, and since the physician disdained the surgeon, the surgeons too had their menials. Thus arose the barber-surgeons—originally *barbitonsores*—who owed much of their prosperity to the fact that monks were forbidden to wear beards. To them were assigned the tasks of bleeding, cupping, leeching, giving enemas, and sometimes of extracting teeth. The relative standing of the physicians, surgeons and barbers may be inferred from an order issued during a plague epidemic in 1383, when for visiting the sick 300 pounds

was to be paid to the physician, 120 pounds to the surgeon, and 80 pounds to the barber.

The union of the Barber Company with the small and exclusive Guild of Surgeons in 1540 under Henry VIII saw the birth of this great College. Over 200 years later, through the good offices of Mr. Ranby, sergeant-surgeon to George II, the surgeons were formally separated from the barbers; in 1800, a further charter from George III founded the Royal College of Surgeons of London, which in 1843 became the Royal College of Surgeons of England.

To summarize, there existed from the 13th century to the 18th, with strife and rivalry of unabated fervour, the physicians, and two specialties born of expert craftsmanship—the surgeons and the barbers. The physicians spent their time wrangling amongst themselves about fantastic theories of disease and methods of treatment. They united only in their determination not to carry out even the most trivial surgical procedure. (Even as late as the 1920s there were many F.R.C.Ps. who would not themselves perform a lumbar puncture or paracentesis.) But in addition to these crafts, the quack—the lens coucher, the herniotomist, the lithotomist and others—still flourished.

Attempts had been made in some places to incorporate those " irregular " healers in existing guilds and companies, primarily for economic reasons. During the 16th and 17th centuries the Barber-Surgeon's Company of London granted temporary licences upon payment of specified fees to cataract couchers, quack lithotomists and herniotomists and others after a burlesque of an examination. The licence was granted for the performance of specified operations only; for example:

" Whereas James Vanotten and Nycholes Bowlen are this day become humble suitors to this Company to be tollerated and permitted to practize as Surgeons within this Cytie of London for and duringe the space of Three months next ensuinge onely for the couchings of the cataracke, cuttinge for the rupture, stone, and wenne. It is upon consideration of their severall suites ordered by consent of this courte That hee, the said James Vanotten, shall be permitted to practize for the couching of the Catarack, cutting for the rupture, stone and wenne for the space of three monthes next ensuinge without contradiccion or denyall of the Masters or Governors of this Company." This permission was granted " Provided that neyther they or eyther of them shall presume to hange out any banners or signe of Surgery in any place other than where they shall Lye, and make theyre abode within the time aforesaid, or practize in any other poynte of surgery than before is specified without further lycence of the Masters or Governors of this Company for the tyme beinge firste had and obteyned."

Such temporary licences were often conditional on members of the Barber Surgeons' Company being called in as advisers. For instance, Matthias Jenkinson was "examined concerninge his skill in the arte of Surgery and was lycenced to cut for the hernia or Rupture and to touch the catarac, to cut for the wry neck (and) the harelip, provided that he call the present Masters of this company to every such cure, or such of the Assistants as are examined and approved as the said Masters in such case shall appoynt". In addition to payments made for the bond, and to the Masters, payments were expected to be made at each consultation, and since many of these irregular practitioners had large and lucrative practices, the arrangement was usually very profitable. Even so, a temporary licence could be revoked, as indeed happened to Matthias Jenkinson, who, on 20th June 1609, a year after being granted the licence, was "discharged from his practize in surgery for that he hath not observed the articles of his tolleration and for his evell and unskillful practize".

The modern ideas and patterns of specialization date from the 17th and 18th centuries, and arose from the growth of medical knowledge, the concentration of large populations in cities, and social and economic factors. The careful descriptions of "diseases" by Sydenham in the later years of the 17th century were to lead a century later to Morgagni's *De Sedibus et Causis Morborum*, in which the correlation of symptoms with organic pathology was clearly described. The development of hospitals in large centres of populations especially following industrialization, and the consequent opportunities for seeing large numbers of patients with similar patterns of symptoms and similar post-mortem findings, led to a number of foci of interest being delimited within the field of medicine. The names of Bright, Hodgkin, Addison, Parkinson, and many others in the first half of the 19th century, will suffice to illustrate this. Yet perhaps the most important event which led to modern specialization was Wöhler's artificial synthesis of urea by heating ammonium cyanate in 1828. For the first time an organic substance had been derived from inorganic material. Thus was shattered the idea that living matter had its own specific mechanisms, and thus began the investigation of man as a physico-chemical mechanism, to the elucidation of which could be brought all the methods of the chemist and all the instruments of physics. The rapid development of biochemistry and chemical pathology, and the application to the study of physiology of all the instruments of physics, which were themselves being invented with incredible speed, bear witness to the fruits of this mechanistic view. The discovery of X-rays has rendered visible directly, or by means of contrast media, practically every part of the body, and given us new and powerful instruments of therapy. Mirrors have been so skilfully made and illuminated that "scopes" are now available which enable many structures to be examined by direct vision. Galvanometers are of such precision that changes of potential in heart, brain, muscle, etc., can be recorded with remarkable accuracy.

Technological advances have given the surgeon new instruments which, with the improvements in anaesthesia (itself to become in the past two to three decades one of the most progressive specialties), in the control of haemorrhage (in which blood transfusion—another specialty—plays an important role), shock and infection, have enabled him successfully to explore regions until recently closed to him.

But it is not only that knowledge advances well beyond any one man's intellectual grasp or manual skills which leads to increasing specialization. There is in man an inner drive which urges him to seek excellence, often for social prestige and financial reward, but also for self-fulfilment. This leads to progressive restriction of the field of practice, and its size is related to the length of time necessary to acquire special knowledge and skills.

Thus, during the last few decades, specialties have arisen which are based on vastly diverse criteria. Many are *topographical* such as dermatology, ophthalmology, gynaecology, urology, orthopaedics. In others, *age* is the determining factor, as in paediatrics and geriatrics. Sometimes a *single disease* or a related group of diseases suffices for a specialty, as in tuberculosis, venereal diseases, and diabetes and asthma clinics now abound. Again *techniques* may determine specialization, as in surgery and its many branches, clinical pathology, radio-diagnosis and radio-therapy, physical medicine, anaesthesia, psycho-analysis, hypnosis, etc. *Geography* accounts for, though it is largely incidental to, the specialty of tropical diseases. *Preventive medicine* is an ideology and the only one not concerned with the cure or alleviation of disease. For some, *medical administration* is a specialty.

As the years have advanced there have been many splinterings from general medicine—cardiology, neurology, haematology, allergy, endocrinology and others; and surgery has witnessed the exclusive practice, not only of orthopaedics, but of neurosurgery, thoracic and cardiac surgery, plastic surgery, genito-urinary surgery, etc. Again, since splintering inevitably tends to leave gaps, new specialties are devised to bridge them, for instance, social medicine. This list is by no means exhaustive, but from it flow certain clear generalizations.

First, the pattern and content of a specialty cannot be constant or rigidly defined. As knowledge advances other specialties branch off from the parent specialty; for instance, the scope of general surgery has contracted by the secession of such specialties as orthopaedics and chest surgery. For the cynic, the general surgeons are now sustained by the crumbs of the surgical cake which remain after the specialties have had their share; but the truth is that they are the custodians of the general principles of sound surgery to whatever part of the body they may be applied—indeed, in this sense, every surgeon should be a general surgeon

with a special interest. Both place and time might vary the content of a specialty. In different countries orthopaedics covers a varying field; in France, in the early part of this century, orthopaedics was restricted to the surgery of childhood (as in the days of Nicholas Andry's *Orthopaedia*); in Germany, it was at that period already a specialty in its own right dealing with deformities at all ages; whilst in Great Britain, until after the first World War, fractures, dislocations and deformities were all part of the work of the general surgeon. Again variations in the incidence of disease alter the content of a specialist's field. The virtual disappearance of rickets, the remarkable lowering of the incidence of bone and joint tuberculosis and of chronic osteomyelitis, the increasing numbers of paralytic poliomyelitis victims, and the rapid rise in motor transport, have all strikingly changed in the last thirty years the pattern of orthopaedics.

Secondly, " pure " specialties do not exist. No specialty is independent of the general field of medicine. The orthopaedic surgeon may see the fractured clavicle which heralds cancer of prostate or thyroid, or the fractured tibia of tabes dorsalis; to him may be referred the patient with the bone changes of hyperparathyroidism or of renal disease. Historians will reflect on the confined outlook of a particular specialty which for so long regarded lupus erythematosus and sarcoid as skin lesions only, and osteitis fibrosa cystica and osteomalacia as primarily disease of bone. Bernard Shaw had the heart of the matter when he wrote that " the pure specialist is in the strict sense of the word an idiot ".

It is not surprising that specialization in any field has attracted much criticism.

The trend of Man's behaviour is, as Trotter emphasized, towards a herd uniformity. To attain by intense effort and concentration an expert competence in a limited field disturbs this trend and tends to isolate the specialist from the common man. This leads to a general denigration of specialism, exemplified in the maxim—" Never trust the expert "—which plays so important a part in the legal and political life of this country. Yet paradoxically there is a widespread proclivity to accept the views of an expert in any one field as carrying great weight in fields in which that expert has no special competence. The views on nutrition of a Nobel prizewinner in physics may be respected, but must not be regarded as being necessarily of the same authority as his statements on his particular field of physics. No living man is likely to merit Conan Doyle's epitaph on Sherlock Holmes in *His Last Bow*: " All other men are specialists, but his specialism is omniscience."

Specialization is an inevitable outcome of advancing knowledge which none doubts has made an indispensable contribution to the health and happiness of mankind. What in the field of medicine are its dangers?

First, that specialization may prevent the "holistic" approach to health and illness. Man is greater than the sum of his parts, much as a masterpiece of music is greater than the orchestra and the score; the conductor knits the work into a whole. So man when ill needs more than a congeries of specialists.

Secondly, by concentrating exclusively on one small part of a field the rest can, in practice, become irrelevant, and thus too often the specialist distorts the patient's disability so as to relate it to his own specialty. Many a uterus—slightly abnormal though unoffending—has been removed for low backache, due to skeletal causes; many a futile cholecystectomy has been performed because a gall-stone has been found in a victim of myocardial ischaemia; and even the orthopaedist has been guilty of treating the stiff back of Parkinsonism with a spinal support.

Thirdly, there is a risk that for the specialist a means becomes an end. The surgeon instead of being the master of his techniques becomes their slave. He may take such pride in their performance that he makes occasions for their use. It is perhaps natural that he should seek to exercise a skill which has cost much in time and energy to acquire. But this too often leads to a bias, born of intellectual blindness, in assessing its value. The history of colectomy for "auto-intoxication", and of nephropexy for the whole range of mental and physical illness, are amongst the relevant examples which cloud the brilliant history of 20th-century surgery. Here I may be excused from repeating as apposite a warning, from my Moynihan Lecture in this College in 1949, about total pancreatectomy for idiopathic hypoglycaemia : "The feasibility of an operation is not the best indication for its performance." Only the circumstances of this lecture lead me to refrain from a detailed elaboration of the application of this text to, for instance, the reconstructive surgery of deformities and the extensive operations for disseminated malignant growths. Fortunately, the tendency is self-correcting; it goes too far for its own good. Only for a limited time "can ignorance conceal itself in techniques and pedantry masquerade as art".

The diagnostic specialties present hazards not for their practitioners only, but alas! for others who place too much reliance on them. The X-ray film and pathological report do not lessen the need for a careful appraisal of the whole patient by history-taking and physical examination. These are time consuming, hence the search for the short cuts to diagnosis provided by radiology, clinical pathology and the like. Perhaps also man's subconscious mistrust of his own observations, especially when they lack precise measurement, leads him to an unwarrantable reliance on the quantitative data, however imprecise, given by instruments. This is true, not only in a positive sense, but also in a negative. The specialist may become so impressed with the powers of his instruments or techniques

that he is not prepared to accept that they can ever fail him. Hence many a carcinoma of stomach or bronchus, even when the clinical picture alone would justify exploration, have been allowed to advance to an inoperable stage because of a negative X-ray; and how often has cardiac infarction been overlooked because of a negative electrocardiogram or serum transaminase test?

It is not only in the practice of medicine but also in medical research that problems of specialization arise, though to these only brief reference can here be made. The best research stems from man's innate and impelling curiosity. The central problem of research is to understand Nature, yet much research is rightly directed to the control of Nature by harnessing her forces—both external and internal—for good.

The researcher today must compensate for lack of width by increased depth. The specialist, it is true, is more likely to breach the ramparts of the citadels which hide Nature's secrets. " Divide and conquer " has been science's clarion call. Yet big discoveries in medicine have often been the result of " bridge-work ", as Burden Sanderson was so fond of saying, or by the genius who observes a single theme in the diversity of facts which has escaped others. But specialization has brought into medical research a scientific snobbery which is to be deprecated. Those who observe man in health and disease, who seek out novel recurring patterns of disease and the effects of treatment, or who faithfully record the natural history of disease are regarded as scientifically inferior to those who use instruments and techniques—of almost incomprehensible complexity—to investigate a small and isolated part of him. But worthy and relevant information from any source is equally precious. The pure mathematician, juggling with numbers and equations, finds consolation in that his work is of " no damned use to anyone ". He looks down on the physicist, who in turn patronizes the chemist. But all of these, and most biologists too, wrote the distinguished chemist, G. N. Lewis, " join together in their contempt for the pariah who, not through a glass darkly, but with keen unaided vision, observes the massing of a thundercloud on the horizon, the petal as it unfolds, or the swarming of a hive of bees. And yet sometimes I think that our laboratories are but little earthworks which men build about themselves, and whose puny tops too often conceal from view the Olympian heights; that we who work in these laboratories are but skilled artisans compared with the man who is able to observe, to draw accurate deductions from the world about him."

How can we minimize the dangers of specialization, especially that of not seeing the wood for the trees?

One consideration is paramount, namely, to inculcate the " holistic " attitude early in the student's clinical training. Let us who are teachers lay sound foundations, not only of basic knowledge, but also of straight

thinking on how to apply general knowledge to a particular problem. Wisdom and judgment will then come with experience if the will be there to profit thereby. With a widening range and complexity of knowledge and the limitations of the human mind, this is indeed the only hope for the future doctor.

Yet it is in teaching that the baneful effects of specialization have been strikingly evident. Instead of our curriculum being educational, it was designed by statute to produce the "complete doctor", giving him smatterings of all extant knowledge. When a new specialty appeared it was "accreted" on to the curriculum, which eventually became—in the words of Cromwell's description of the laws of England—"a tortuous and ungodly jumble". Unlike the older single-author textbooks, our modern textbooks for undergraduates lack a general philosophy of medicine; they too often comprise unrelated monographs of multiple authorship. Thus, instead of a tapestry of clear and purposeful design, they resemble a patchwork quilt. We can but pray that the greater flexibility of the recent recommendations of the General Medical Council will correct this error.

The clinical material with which the undergraduate pursues his undergraduate studies is generally over-specialized. The population of our undergraduate teaching hospitals too often reflects the narrow interests of those in charge. To spend three months clerking or dressing and seeing virtually nothing but hypertensives or enlarged prostates is not only soul-destroying, but deprives undergraduate education of its meaning and purpose. It is not to the student's training only, but to that of the specialist, both as practitioner and as a teacher of undergraduates, that these comments apply. Specialists must be grounded in, and competent to apply, general medical and surgical principles in the restricted context of their specialty; in teaching they must stress γνωσις—knowledge and understanding—and not simply τεχνη—the minutiae of their special techniques.

Another contribution to avoiding the unwelcome consequences of specialization in medical practice is to have someone in continuing charge of the patient. Outside hospital, and with most patients, this must and should be the general practitioner. But in hospital it is the specialist. Yet, there is too often in hospital the attitude that the specialist should not act as a personal doctor, but simply make his specific contribution to the patient's immediate needs. From this lack of overall control flow the baneful effects of divided responsibility. This is particularly true when the patient's problem demands a team of specialists. Yet these are admittedly essential to the proper care of many patients.

Team-work is perhaps even more necessary for medical research. Here not only specialists in medicine, but those in any scientific discipline may

make a contribution to healing. The problems, for example, of the metallurgist, macromolecular chemist, and the isotope expert, are of current and impressive interest for the orthopaedic surgeon. Only by team work at this level can the divergent specialisms of knowledge lead to convergence in unifying principles and rewarding techniques, and—dare I say it?—may lead to such narrowing of content of a discipline that, by the pursuit of prevention and positive health, the discipline may itself disappear in part or in whole.

We in this country have an unrivalled opportunity under the Nationa. Health Service to ensure that our specialties develop along the right pathsl Economic considerations need no longer blunt the growing edge of a specialty as happened, for example, with paediatrics and neurosurgery only a few decades ago. No specialist need misuse his apparatus to stake a claim to remunerative practice based on the worship of the machine by a gullible public—examples of which will crowd in on the more senior members of my audience. Again, for those who are so minded, a career in clinical research is now open. And in most of our hospitals there exist unrestricted opportunities for team work of the most productive kind. These openings create the challenge of the synoptic view of man. Let us see that we prove worthy both of our opportunities and of our responsibilities.

I fear that I have exceeded my time, and done scant justice in this lecture to him whom it seeks to honour. Yet I believe it reflects his philosophy. Nicholas Andry derived orthopaedics from ορθος = straight and παιδιον = a child. I believe that Sir Reginald with the elder Sayre would derive orthopaedics from ορθος and παιδευω = to educate. It is within this concept of orthopaedics that I have chosen to reflect on specialization in medicine, and thus to pay tribute to a friend and colleague; an acknowledged leader, not only in his specialty, but in many fields whose purpose is the betterment of his fellowmen; an outstanding teacher and writer, imbued with the concept of holism; and an ambassador of goodwill, whose name and work are known and praised the world over. Few in our profession can equal, and none surpass, his claims to Dr. Johnson's epitaph on Goldsmith: "*Nullum quod tetigit non ornavit.*"

FACULTY OF DENTAL SURGERY

Election to the Board

As the result of a ballot for the election to the Board of two Fellows in Dental Surgery on Friday, 17th June, Professor G. L. Roberts (Sheffield) and Professor H. H. Stones (Liverpool) were re-elected for further periods of service.

THE DISSEMINATION OF CANCER CELLS DURING OPERATIVE PROCEDURES

Hunterian Lecture delivered at the Royal College of Surgeons of England

on

30th March 1960

by

John D. Griffiths, M.S., F.R.C.S.

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SINCE THE DAYS of John Hunter, there have been great advances in the methods of research, due to the technical progress made by modern science. In Hunter's day, the main tool of the research worker was his own ability to observe and record what could be seen with the naked eye and with the limited microscopical instruments then at his disposal. Indeed, it is to such men that science owes its heritage, for many of their observations have been confirmed by the elaborate technical methods now in use. Perhaps one of the most striking differences in such work today may be seen in cancer research, where the vastly increased knowledge of its biochemical and cytological background has resulted in the development of the research team, composed of experts in their own fields. It was my privilege to work with such a team, who have been investigating the dissemination of cancer, with a special interest in the effect of surgical treatment on dissemination and the possible methods of increasing the value of operative techniques with the use of anti-cancer drugs.

With the great advance in modern surgery, the extent of surgical resection in carcinoma has been carried to its anatomical limit. Although in some fields the results of radical surgery have been encouraging, it is clear to most surgeons that, such is the nature of neoplastic dissemination, it is impossible to eliminate the disease from the whole body in a large number of patients by radical surgery.

In recent years, renewed interest has been taken in the mechanism by which dissemination of cancer occurs following operative procedures. The commonest ways in which the spread of malignant cells can occur during surgery are through implantation of the neoplastic cell at the site of operation and through the entrance of cancer cells as emboli into the blood stream.

Implantation of malignant cells

Ryall in 1908 drew attention to the dangers of dissemination of cancer by implantation and used the term " cancer infection ", which describes well the danger of contamination of operative wounds by malignant cells.

The hazards of the free cancer cell were apparent to such great masters of surgery as Sampson Handley and Sir Ernest Miles, and it was these men who first introduced the concept of adjuvant chemotherapy during surgical operations; they both used mercury perchloride to wash the wounds following resection—Miles following his abdomino-perineal resection of the rectum, and Sampson Handley following radical mastectomy.

In a recent survey of cases operated upon for carcinoma of the breast, rectum and colon at St. Bartholomew's Hospital, London, between 1947 and 1952, and subsequently followed up for 5 years, the incidence of local recurrence was found to be 10 per cent. in carcinoma of the breast (Whittle *et al.*, 1960), 10 per cent. in rectum and rectosigmoid and 9 per cent. in carcinoma of the colon (Griffiths *et al.*, 1960) (Table I). In these cases, curative operations were attempted at the time of surgery. This indicates the hazard of local dissemination, although at the time of operation there is no visible evidence of its presence.

TABLE I

LOCAL RECURRENCES AT ST. BARTHOLOMEW'S HOSPITAL (1948–1952)

Five Year Follow-up

Site	*No. of Cases*	*No. of Local Recurrences*	
Breast	472	45	10%
Colon	112	10	9%
Rectum	175	17	10%

One of the major advances in operative technique in carcinoma of the colon and rectum is recognition of possible implantation of malignant cells into the anastomosis following a resection. Naunton Morgan and Lloyd-Davies (1950), in this country, drew attention to the possible cause of local recurrence following anterior resection of the rectum being due to implantation of malignant cells in the anastomosis and described a technique using mercury perchloride 1 in 500 to swab out the proximal colon and wash out the rectal stump from below before the anastomosis is performed. In America, Cole (1952) drew attention to a local recurrence rate of 16 per cent. in 55 consecutive patients having resection for carcinoma of the colon and proximal rectum over a five-year period at the Illinois Research Hospital; of these, 10.9 per cent. were recurrences by implantation at the site of anastomosis. Cole suggested that intraluminar dissemination of the growth during surgical procedures could be prevented by placing ties above and below the tumour in the colon before any manipulation was performed, the clamps being placed beyond the ties during the resection. McGrew *et al.* (1954) demonstrated by cytological technique that manipulation of the growth disseminates free cancer

cells along the lumen of the bowel and that the procedure described by Cole was effective in preventing contamination of the distal and proximal ends of the colon by malignant cells at the site of the anastomosis. Cole also advocates washing the proximal and distal loops with distilled water before performing the anastomosis. The effectiveness of these principles can be gauged by the successful diminution of local recurrences that has occurred in the operation of anterior resection for carcinoma of the rectum. Goligher *et al.* (1951) reported 23 local recurrences in 162 cases of resection of the rectum with anastomosis or Hartmann's procedure; in half of these recurrences there was strong evidence that implantation had occurred at the site of anastomosis during the operation. Morgan (1958), in a personal series of 136 cases of anterior resections in which the rectum had been washed out with 1 in 500 mercury perchloride, reported a local recurrence rate of only 1.5 per cent.

TABLE II

LOCAL RECURRENCES IN CARCINOMA OF THE RECTUM

Number of Cases	175	
Number of Recurrences	17	10%
Number of Anterior Resections	23	
Number of Recurrences	1	4%
Number of Excisions	152	
Number of Recurrences	16	11%
Extra Rectal Spread found at Operation	8	5%

In 112 cases of carcinoma of the colon operated upon at St. Bartholomew's Hospital between 1947 and 1952 (Table II) 10 developed local recurrences within five years. Of these, three were found to be at the site of the anastomosis. Over the same period, 23 cases of carcinoma of the rectum were treated by anterior resection and one (4 per cent.) developed local recurrence at the anastomosis. In 13 of the 23 anterior resections, the distal rectum was washed out with 1 in 500 mercury perchloride, but the case in which the local recurrence occurred had not been treated in this way.

Excision of the rectum was performed in 152 patients and local perineal recurrences occurred in 16. Of these, eight were shown to have perirectal spread at the time of operation and seven had no demonstrable extra-rectal involvement. In one case of local recurrence the rectum was perforated during the operation with consequent contamination of the perineum by faeces and malignant cells. At the period during which these excisions were performed no "anti-cancer cell" measures were routinely used in the perineal wound.

It is often difficult to separate implantation from local recurrence, but where adequate normal tissue has been removed at operation, as proved by histological examination of the specimen, it can be assumed that a recurrence at the site of operation is due to implantation of malignant cells. This is even more certain when the recurrence occurs at a suture-line or in the scar.

Circulating cancer cells

The dissemination of the cancer cell through venous channels has for a long time been postulated and venous invasion by growth often demonstrated histologically. Ashworth in 1896 reported cells in the blood after death which resembled the cells seen at post-mortem in a patient dying of a malignant skin tumour, and Ward in 1913 reported numerous large cells in the peripheral blood of a patient a few hours before dying of a carcinoma of the stomach. Pool and Dunlop (1934) examined the peripheral blood of 40 patients having malignant disease, and although they describe atypical cells in 17 of the cases they did not positively identify these cells as cancer cells. Isolation of the circulating cancer cell in the general circulation of a live patient with malignant disease was first performed by Engell (1955). This was followed by Roberts and his co-workers (1958), who developed a technique for the separation of the elements of blood, which allows the use of the Papanicalaou stain to identify malignant cells. Long *et al.* (1959) have further simplified their techniques and have in all, using both methods, examined the blood of 506 subjects for circulating cells. Of these, 178 were investigated by Long's method and 328 by Roberts'.

In 328 patients investigated using the original technique described by Roberts *et al.*, and reported by Long *et al.* (1960), the patients were divided into " curable " and " incurable ". This is an arbitrary classification based on a surgical assessment at the time of operation: if the patient's tumour was completely removed he was classified as " curable "; if growth was known to have been left, including distant metastasis, the classification was " incurable ". In the curable group—representing all types of carcinoma—20 per cent. had positive cancer cells demonstrable in the blood obtained from the anti-cubital vein, while 29 per cent. of the incurables showed cells. In reporting the results of the simplified isolation technique, Long *et al.* (1960) gives the percentage of " curable " with malignant cells in peripheral venous blood as 25 per cent. and " incurable " 39 per cent., in 178 patients examined. In 69 patients in which blood was obtained from veins draining the site of the tumour, 28 per cent. were found to have circulating malignant cells in the " curable " cases and 37 per cent. in those classified as " incurable ".

It can be assumed that the percentage of patients who have in fact circulating cells is much higher than those reported above, as the technique

for their isolation is difficult and there is a possible loss of some cells during the separation technique. The significance to be attached to the presence of the circulating cell is not yet known. Engell recently reported the follow-up for five to nine years of his original cases and concluded that there was no overall difference in the survival figures of patients in whom cancer cells were found and those in whom they were not demonstrated.

There is in the body a resistance to the implantation of the malignant cell, which has been termed " host resistance " by the older pathologist. An interesting observation has been made by Roberts and Long that in all the cases of carcinoma of the gastrointestinal tract, i.e. drained by the portal vein into the liver, positive peripheral circulating cancer cells have only been demonstrated in cases where there has been spread of the tumour outside the organ of origin, i.e. there would be drainage into the systemic circulation as well. It has been previously shown by Cole *et al.* (1954) and later by Fisher and Turnbull (1955) that, in carcinoma of the colon, blood from veins draining the site of the tumour often contains cancer cells (Fisher and Turnbull report 31.4 per cent.). This implies that the liver in some ways plays a part in destroying or removing the cell from the portal circulation before it enters the systemic vein; the fate of the cell then depends on whether it can implant and grow or be destroyed.

Circulating cancer cells during surgery

The possibility of dissemination of cancer cells via the bloodstream during operative procedures has been considered for many years. Long *et al.* (1960) investigated the response of 57 patients with malignant disease to operative procedures by examining their blood before, during, and after operations involving resection of the neoplasm. They describe three responses to operative procedures which may occur. In the first group of patients, the pre-operative blood samples taken showed no circulating cancer cells, but during the operation cancer cells were recovered from the circulation, only to disappear after removal of the tumour. This occurred in eight (14 per cent.) of the 57 patients. The second group of five patients (9 per cent.) were those in whom pre-operatively malignant cells had been detected in the circulation; at operation, there was an increase in the number of cells in each sample, but following removal of the neoplasm no circulating cells could be obtained. Three patients (5 per cent.) in the third group showed cancer cells in the blood before and during the operation, and a subsequent fall in the number of cells found immediately post-operatively, which again increased during the first and second post-operative days. In this last group the patients were classed as " incurable ", having non-resectable or inadequately removed disease. In the remaining 41 (72 per cent.) patients examined, no cancer cells were found in the blood at any time. This does not mean that they were not present in the circulation, as the techniques for detection are still limited in their accuracy.

It has therefore been well substantiated that cancer cells appear in the general circulation in a number of patients with neoplastic disease, and that surgical procedures and manipulation of the primary growth tend to produce showers of cells in the blood stream. What of the fate of the cancer cell? Earlier pathologists concluded that there was a resistance in the body to vascular dissemination. Goldman (1897) concluded that since the invasion of veins was a common finding in post-mortem, but yet a number of organs remained free from metastasis, there existed in the body some " protecting substance " giving a resistance to the cancer cell. The nature of this mechanism has eluded the research workers in this field for over sixty years, but the conclusions of Goldman have recently been re-amplified by Engell (1959), as stated previously, who followed up cases from whose blood he had isolated cancer cells five to nine years previously and found no difference in the survival rate compared with similar groups of patients in which he had failed to demonstrate circulating cancer cells. But cancer cells have been known to lie dormant for many years, as pointed out by Hadfield (1954), who maintains that secondaries which develop two or more years after adequate excision of the primary growth cannot be due to malignant emboli or circulating cancer cells. The period of dormancy can be from 6 to 20 years, as demonstrated by Gordon Taylor (1959), who quotes from his own long experience a personal case of one recurrence which occurred 17 years after radical mastectomy. It therefore cannot be assumed that circulating cancer cells are all destroyed, but it must be assumed that they are all potentially capable of forming secondaries. Any surgical procedure which will increase the number of circulating cells is therefore increasing the danger of dissemination and cannot be ignored.

The fate of the circulating cancer cell

The fate of the circulating cancer cell has been investigated by many. Schmidt (1903) studied the lungs and pulmonary vessels of 41 cases of carcinoma of the abdominal viscera and found malignant nodules in 15 cases. He stressed that few of these gave rise to pulmonary secondaries since the fibrous reaction, which occurs in the vessel wall, results in the death of the neoplastic cell. He also drew attention to the importance of organization of the thrombus in providing new vascular connections for the developing metastasis. Levin and Sittenfield (1911) showed that the number of lung metastases found after intravenous injection of transmittable tumours in rats and mice was low, although the tumour grew satisfactorily following subcutaneous injection. They confirmed Schmidt's finding that many tumour emboli had been destroyed in the pulmonary vessels. Takahashi (1915) emphasized the effectiveness of the vessel endothelium as a barrier against extravascular spread and demonstrated, using mouse tumours, that before the cells disappeared from the blood, they became vacuolated and surrounded by leucocytes. The

histogenesis of metastasis produced by the T150 tumour in C57 black mice has been well described by Baserga *et al.* (1955), who showed that the cancer cells form small emboli of five to six cells, which adhere to the wall of the pulmonary arterioles. They postulate that there is an intravascular growth of the cells before extravascular spread occurs.

In all previous reports on intravascular spread, great emphasis has been laid on the occurrence and importance of the tumour emboli, but the fate of the single circulating cell has not been investigated. Experiments have been performed to demonstrate this, using intravenous injection of Walker 256 tumour in rats. The Walker tumour was made into a sterile suspension of single cells by passing through a cyto-sieve, as described by Snell (1953). The number of cells in the suspension was counted in a

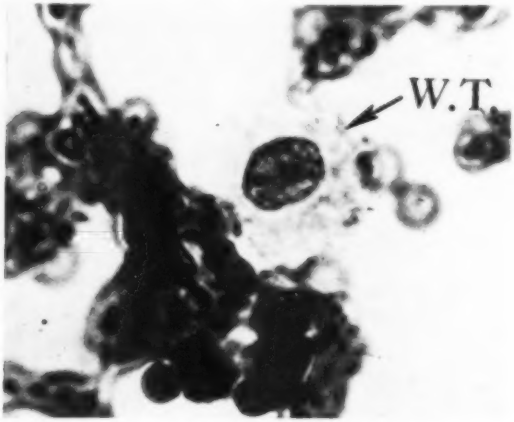
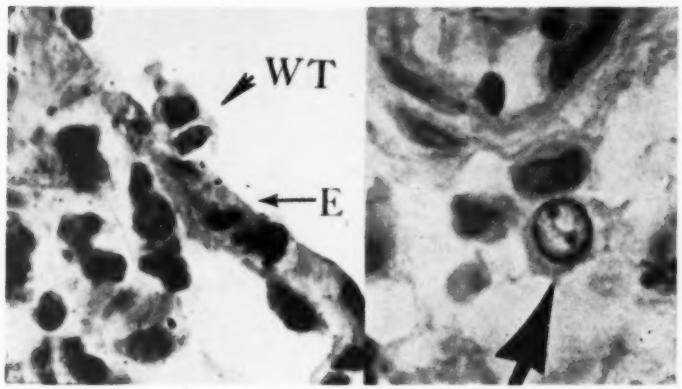


Fig. 1. Walker 256 carcinosarcoma cell (W.T.) isolated from rat's blood using Long's modified streptolysin technique 60 minutes following intravenous injection of tumour suspension.

counting chamber and diluted until 1 c.c. contained 100,000 viable cells. Adult female rats were then taken, the back leg shaved and 1 c.c. of the suspension injected into the saphenous vein, care being taken to prevent any extravascular spill.

In one group of rats, cardiac puncture was performed to obtain blood from the left ventricle at 5, 10, 15 minutes and then every 15 minutes after injection for two-and-a-half hours. One c.c. of blood was obtained at each cardiac puncture, but rarely did one rat survive more than three punctures. It was therefore necessary for a number of rats to be injected with the same suspension simultaneously. The blood samples were then treated by the method described by Long *et al.* (1959) and examined for

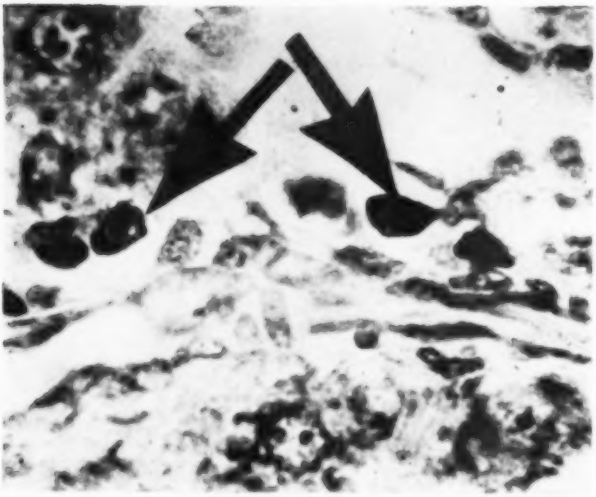
circulating Walker tumour. (One modification of the technique as described for human blood is that 9 c.c. of streptolysin must be used for 1 c.c. of rat's blood to produce haemolysis of the red cells.) In this way it was possible to trace the number of circulating cells over the period of the experiment. During the earlier samples up to one hour, only a few circulating cells could be found, but following this the number increased and was maximal at 90 minutes. An examination of blood taken 24 hours after intravenous injection revealed no circulating tumour cells (Fig. 1).



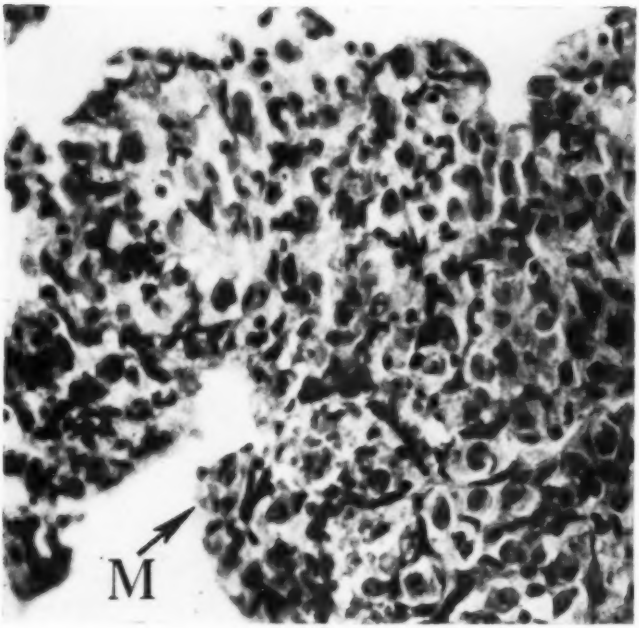
(*a*) (*b*)

Fig. 2. Histological sections from rats following intravenous or intraportal injection of cell suspension from Walker 256 carcinosarcoma. (*a*) Section of lung taken immediately following intravenous injection of cell suspension, showing the attachment of the Walker cell (W.T.) to the endothelium of the pulmonary vessel. (*b*) Section of lung five minutes following intravenous injection, showing Walker tumour cell having become extra-vascular. (*c*) (*see page* 22) Section of liver five minutes following intraportal injection of tumour suspension, showing extra-vascular tumour cells. (*d*) Section of lung 10 days following intravenous injection, showing development of metastasis in the interstitial tissue of the alveolar wall. (*e*) (*see page* 24) Section of liver from same animal as (*d*) showing extra-vascular metastasis (M) around a hepatic vessel (V). (*f*) Section of lung 30 days after intravenous injection of Walker tumour, showing a large metastasis having developed around a pulmonary vessel (V).

The second group of rats was injected as described with the same number of Walker tumour cells intravenously, but they were sacrificed at set times and their lungs and liver removed, placed immediately in a fixative and then submitted for serial histological section. In this way the fate of the cells in the tissues could be followed by sections taken at intervals varying from five minutes to five weeks following after injection. A third group of anaesthetized rats was injected intraportally following coeliotomy, the lungs and liver being removed after 5, 10, 15 and 30 minutes and immediately fixed and submitted for serial histological section.



(*c*)



(*d*)

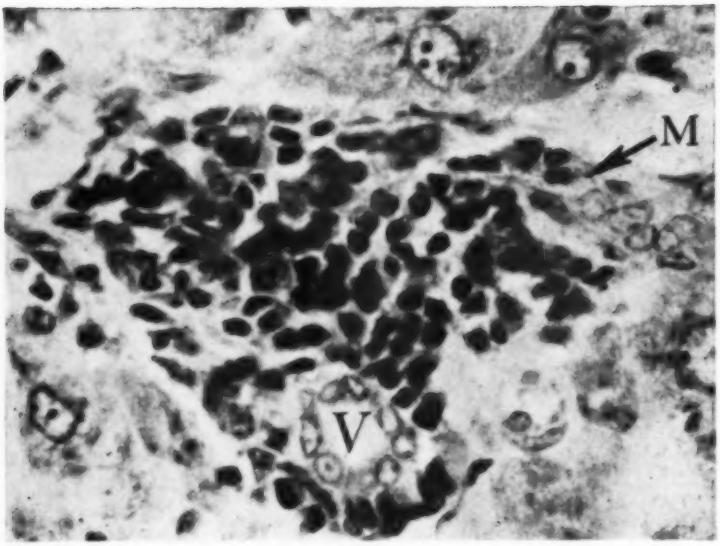
From the examination of the histological sections a number of interesting findings were noted. It was demonstrated that the tumour cells attached themselves to the endothelium of the walls of the arterioles in the lung and soon passed through to become extravascular, being identified in the interstitial tissues within 5 minutes. Examination of sections of the liver in animals having had intravenous injection of the tumour suspension also revealed extravascular tumour cells, indicating that the cells had passed through the pulmonary capillary bed, entered the portal system and then passed into the liver tissue. In some sections of the lungs, tumour cells could be seen passing through the capillaries and arterioles. It is difficult to determine the exact difference between the arteriolar and capillary plexuses in the lung tissue, except in the alveoli where the capillaries are very thin. Following intraportal injection of the tumour suspension, cells could be seen in the liver vessels but the majority were extravascular, lying in the centre of the liver lobules. Sections of lung of the same animal show the cells having passed into the interstitial tissue of the lungs (Fig. 2).

If the rats are injected intravenously with Walker tumour suspension and allowed to live for one month and then sacrificed, multiple tumour metastases can be seen in the lungs. The liver, however, appears normal on naked eye examination, but tumour cells can be seen microscopically.

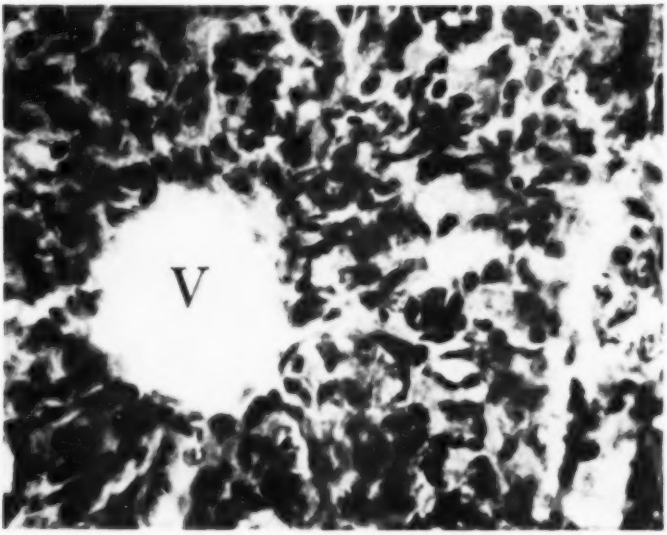
Histological sections of both lungs and liver taken from animals sacrificed between six and 14 days following injection showed that the development of tumour in the lung is much more advanced and the secondaries are bigger than in the liver. This is contrary to what was found by Lucke *et al.* (1952), who injected V2 carcinoma cells into rabbits intraportally and intravenously simultaneously, and found that the liver developed tumour five times larger than the lung. In the case of intraportal injection of Walker tumour in rats, the lungs rarely show metastases although, as shown previously, malignant cells can be demonstrated in the lung tissue.

It must be assumed that the cancer cell has, in some way not yet understood, lost some of its virulence during its passage through the pulmonary capillary plexus, although the circulating cancer cells which have been demonstrated in the blood 90 minutes following intravenous injection are still capable of producing tumours. This has been proved by subcutaneous inoculation of blood from one of these rats into a control, a tumour being produced at the inoculation site in three weeks.

Not all the cancer cells which circulate in the blood stream produce metastases (Fig. 3). Some are undoubtedly destroyed in the circulation by the elements of blood, as described by Takahashi, although Warren and Gates (1936) disagree with this and have shown that blood does not inactivate tumour suspension. The larger emboli of tumour cells will get trapped in the capillary system of either the lungs in the systemic circu-



(e)



(f)

lation or the liver in the portal system; these either grow or are destroyed and form hyaline thrombi. Other cells become attached to the endothelial lining of the capillaries or arterioles and then either pass through the vessel wall and become extravascular, or become free again and rejoin the circulation. Of the cells that become extravascular, some will form secondary metastases, the rate of growth depending on the nutrition available and the host resistance; others are undoubtedly prevented from dividing and die, and are dealt with by the endothelial system.

Many unknown factors are involved in the fate of the circulating cancer cell, one of the most important being its own virulence. This may be affected by the antigen-antibody reaction between the cell and its host,

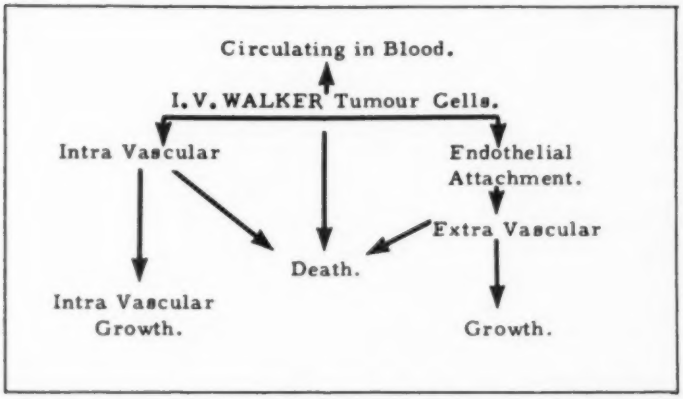


Fig. 3. Diagram illustrating the fate of cells injected into the circulation.

and the factors which ultimately decide whether or not a tumour cell becomes established may well be governed by this reaction, of which very little is known as yet.

Host resistance

In recent years, the energies of the pathologists, cytologists and biochemists have been directed towards investigation of the nature and causation of the change in the normal cell which produces malignancy. The ultimate treatment and cure of cancer may well be found in the laboratory, but for those who deal with patients who have the disease there is another important consideration. It is the effect of the host on the neoplastic cell, and I feel this side of the " cancer " problem has been neglected for many years. Sir Gordon Gordon Taylor (1959), in his Mitchell Banks lecture, drew attention to the variation which exists in the resistance of patients to disease and the way in which carcinoma cells can be dormant for many

years and then be brought back to activity by some disturbance of the patient's general health, such as operation or trauma, causing a general reaction which we have come to look upon as a " stress " reaction.

In the following experiments, I will endeavour to present some basic physiological responses which affect the host resistance and which may have a bearing on the surgical treatment of the patient suffering from neoplastic disease.

The influence of surgical procedures on the increased susceptibility of animals to the implantation of malignant cells has been demonstrated by Buinauskas *et al.* (1958), Lewis *et al.* (1958) and Fisher *et al.* (1959a). They have demonstrated that surgical procedures produce an increased susceptibility in the rat to the inoculation of transmittable Walker tumour.

In repeating these experiments in a modified form, the effect of surgical operation on the development of pulmonary metastasis following intravenous injection of tumour cells has been demonstrated. Two groups of mature female rats were taken and kept under identical environmental conditions. One group was then anaesthetized and a laparotomy performed, the intestines being left outside the peritoneal cavity for 30 minutes and traumatized by rough handling before being replaced. During the period of the experiment, 100,000 fresh Walker tumour cells were injected intravenously into the saphenous vein of both the operated group and a control group of anaesthetized rats which had not been subjected to surgical trauma. Both groups were sacrificed after 21 days and their lungs removed and examined macroscopically for secondaries. In the control group, metastatic nodules could only be seen in 15 per cent.; in the operated group, metastases were visible in 65 per cent. of the specimens (Table III). Histological section of the lungs in both groups showed evidence of growing cancer cells, but the rate of growth in the operated rats was more rapid and hence the higher percentage of visible macroscopic secondaries.

TABLE III

EFFECT OF OPERATIVE STRESS ON METASTASIS IN LUNG

Groups	*No. of Rats*	*% Macroscopic Secondaries*
Operative Stress	26	65
Control	26	15

I.V. 100,000 Walker 256 Tumour Cells.
Rats sacrificed after 21 days.

In further investigating this response, which can be considered to be due to surgical " stress ", experiments were performed using non-traumatic forms of stress induced by subjecting rats to extreme temperatures, to which they had not been acclimatized, for a period compatible with their survival. These types of " stress " can be considered to be metabolic in

nature, as they alter the metabolic rate of the animal by inducing physiological changes due to the normal adaptation mechanisms which act during variations in the environmental temperature.

The experiments which have been performed can be divided into two main groups. In the first group the rats were anaesthetized and in the second group they received no anaesthetic or any other form of medication. The physiological reaction in these two groups is entirely different. In the unanaesthetized rat (in Group 2), the mechanism of adaptation occurs, which enables the body to adjust its metabolism within certain limits of the environmental temperatures. In the first group the anaesthetized animal loses all of its adaptation mechanism and tends to assume the temperature of its surroundings, thus, when subjected to low temperatures, hypothermia ensues, and when subjected to high temperatures, hyperthermia is produced. Another difference between these two groups is that in the anaesthetized animal the metabolism is more constant, but during exposure of the normal animal to cold and heat the mechanism varies within the body's needs to maintain its normal temperature. Both groups have been subjected to cold and heat sufficient to produce maximum " stress " reaction compatible with survival.

Rats were subjected to cold and heat " stress ", also to hypothermia and hyperthermia before being inoculated subcutaneously with Walker 256 carcinosarcoma cells. By " cold stress " is meant the response of the unanaesthetized animal to temperatures lower than its normal habitat, but compatible with life, which in most cases did not lower the body temperature. In the hypothermia used in these experiments, the animal was anaesthetized and the body temperature was lowered by external cooling. Similarly, in the unanaesthetized animals subjected to higher than normal environmental temperatures (whose rise in body temperature was only very small) the term " heat stress " is applied; in animals anaesthetized and subjected to temperatures which gave a considerable rise in body temperature, compatible with life, the term hyperthermia is used.

Influences of thermal stress on host resistance

The method used for assessing the host resistance to the malignant cell in these experiments is based on the " takes " of the transplantable Walker tumour in the rats following " stress " as compared with a normal animal (Griffiths *et al.*, 1960). A suspension of Walker 256 carcinosarcoma cells " aged " from 6 to 12 hours at room temperature is prepared by the method described by Lucke *et al.* (1952) and modified by Chan *et al.* (1960). Ageing of the tumour suspension is necessary to diminish the percentage " takes " obtained, since the Walker tumour at the time the experiments were being prepared was so virulent that inoculation of a fresh

suspension of cells would yield " takes " in 100 per cent. of animals. The suspension of Walker cells was injected subcutaneously on the abdomen of the rats, which had previously been shaved. It must be emphasized that during these procedures of making and injecting the " aged " suspensions a full sterile technique must be observed, as infection can cause erroneous results. One half of the rats were inoculated immediately before being subjected to the " stress " and the other half following the thermal stress. The percentage " takes " in each group was calculated after six weeks; the rats not having developed tumours by this time were kept for three months to detect delayed " takes ".

Cold stress hypothermia

The maximum cold " stress " to which adult rats could be subjected was determined by placing the animals in a constant temperature cold room in individual cages. The temperature at which a maximum " stress " was produced for a given time, without producing death through cardiac arrest, was determined. Rats left for six hours at a temperature of 21° F. survived satisfactorily without mortality; if left for eight hours at this temperature there was a mortality of 10 per cent. and at 24 hours it was 100 per cent. A temperature of 32° F. for 24 hours was well tolerated by the rats and it was possible to acclimatize them to this temperature.

Hypothermia was induced by anaesthetizing rats with nembutal (2 mgm. per kilo body weight, intra-peritoneally) and chlorpromazine (1 mgm. intra-muscularly). The animals were then placed in a cold chamber at 32° F. for half-an-hour. The fall of their body temperature was recorded every five minutes by means of a rectal thermometer, the temperature drop being rapid at first, but becoming slower at the end of half-an-hour. When the rectal temperature had fallen to 85° F. the rats were removed and placed in a chamber at 58° F. to prevent the body temperature dropping below 80° F. They were maintained at a body temperature in the region of 80° F., but the temperature was not allowed to fall below 75° F., because cardiac arrest is produced at temperatures below this level. The period of hypothermia lasted for two to three hours, the body temperature then gradually rose and a normal temperature was regained as the effect of the anaesthetic wore off, normally in four to six hours.

Rats subjected to cold for various lengths of time respond by shivering and increasing their intake of food. For the purpose of these experiments convenient temperatures, which would produce maximum stress without producing mortality in the animals, were taken as 32° F. for 24 hours and 21° F. for six hours. Rats can be kept at 32° F. indefinitely without a lowering of their body temperature, but when kept at 21° F. for more than six hours a drop of 2° to 3° in their body temperatures occurs, and hypothermia, with consequent cardiac arrest, ensues. At 21° F. for eight hours

there was a mortality rate of 10 per cent., and when the animals were left in the room at this temperature for 18 hours there was a mortality of 90 per cent.

In 41 rats subjected to a temperature of 32° F. for 24 hours 85 per cent. developed tumours following subcutaneous inoculation of 25,000 Walker 256 cells "aged" 12 hours at room temperature, compared to 53 per cent. in 34 rats kept at room temperature (78° F.). Of 96 rats exposed to a temperature of 21° F. for six hours, 96 per cent. developed a tumour following inoculation subcutaneously of 20,000 cells "aged" six hours, compared to 72 per cent. of 61 rats inoculated with the same suspension but kept at room temperature (see Table IV). In the rats subjected to

TABLE IV

"TAKES" OF WALKER 256 CARCINOSARCOMA IN RATS FOLLOWING COLD STRESS

Type of Stress	*Average rectal temperatures*	*Number of rats*	*% "Takes"*
24 hours at 32° F.	101° F.	41	85%
Controls (Room temp. 78° F.)	101° F.	34	53%
Subcutaneous inoculation of 25,000 cells "aged" for 12 hours			
6 hours at 21° F.	100° F.	96	96%
Controls (Room temp. 78° F.)	101° F.	61	72%
Subcutaneous inoculation of 20,000 cells "aged" for 6 hours			

hypothermia, 92 per cent. of 61 animals developed tumour as compared with 58 per cent. in 29 controls, following subcutaneous inoculation of 25,000 Walker cells "aged" 12 hours (see Table V).

TABLE V

"TAKES" OF WALKER 256 CARCINOSARCOMA IN RATS FOLLOWING "HYPOTHERMIA" (UNDER NEMBUTAL ANAESTHESIA)

Types of Stress	*Average rectal temperatures*	*Number of rats*	*% "Takes"*
Hypothermia for 2 hours	80° F.	61	92%
Controls (Unanaesthetized at room temp. 78° F.)	101° F.	29	58%
Subcutaneous inoculation of 25,000 cells "aged" for 12 hours			

The tumours in the hypothermic animals appeared five to six days earlier and were consequently bigger than those in the control group. Half the rats in the "cold stress" and hypothermia groups were inoculated

before the commencement of the exposure and the other half at the end, but there was no difference in the percentage " takes " in these two groups.

The result of coeliotomy in hypothermic animals was a 100 per cent. " take " in 12 animals, as compared with a 39 per cent. " take " in the 21 control animals. This shows that there was an additive effect of the two types of stress reaction.

Another group of 59 rats of the same age and weight was divided into three groups. The first group of 15 rats was acclimatized at 32° F. and kept under these conditions for two weeks; the second group was placed in the cold room at 32° F. for 24 hours, and 21 rats were kept as a control in a room at normal temperature (78° F.). All three groups were inoculated subcutaneously at the same time, i.e. at the end of two weeks' acclimatization of the first group, with 25,000 cells " aged " 12 hours. The first group was kept in the cold room at 32° F. for an additional three weeks, the second group being taken back to its normal room temperature following its 24 hours' " cold stress ". As can be seen in Table VI, in the

TABLE VI

" TAKES " OF WALKER 256 CARCINOSARCOMA FOLLOWING ACCLIMATIZATION OF RATS TO COLD

Type of Stress	*Average rectal temperatures*	*Number of rats*	*% " Takes "*
32° F. for 24 hours	101° F.	24	100%
32° F. for 2 weeks pre- and 3 weeks post-inoculation	101° F.	15	93%
Control at room temp. (78° F.)	101° F.	21	62%

first group " takes " occurred in 93 per cent. of 15 rats; in the second group, having had the " acute stress ", " takes " occurred in 100 per cent. of 24 animals, the controls revealing " takes " in 62 per cent. of 21 rats. This shows that it is not necessarily the acute nature of the stress which produces the increased susceptibility to the inoculated tumour cell, but the general response of the body to cold, which through increasing the metabolism has also created a more favourable " culture media " for the cancer cell to grow.

The " cold stress " experiment was repeated in 25 rats kept at 32° F. for 24 hours and then kept at normal room temperature for 48 hours, before being inoculated subcutaneously with 25,000 Walker 256 cells " aged " 12 hours, as described above. At the same time, 30 control animals kept at room temperature were inoculated. At the end of three weeks, 20 per cent. of the control animals developed tumours and 25 per cent. of the

" stressed " rats (Table VII). This indicates that the increased susceptibility of the animal to the implantation of the tumour cell has disappeared within 48 hours of the termination of the cold stress. As will be shown later, this corresponds to the fall of the total plasma 17-hydroxycorticoids, indicating that the adrenal response has returned to normal after 48 hours.

TABLE VII

" TAKES " OF WALKER 256 CARCINOSARCOMA IN RATS INOCULATED 48 HOURS FOLLOWING COLD STRESS

Type of Stress	*Number of Rats*	% *" Takes "*
24 hours at 32° F.	25	25%
Controls (Room temp. 78° F.)	30	20%

In the rats subjected to " cold stress " there was no weight loss, but their consumption of food increased from 75 grams per kilo per day at room temperature to 165 grams per kilo per day during " cold stress ", indicating an increased metabolic activity to maintain body temperature. During hypothermia, the weight loss was minimal with an average loss of 3.5 grams per rat. This is comparable to the loss in the unanaesthetized rats deprived of food and water during the period of time the animal was under hypothermia.

Heat stress and hyperthermia

In the heat stress experiments the rats were placed in a chamber kept at 110° F. at a humidity of 60 per cent. for six hours, in individual cages. It was found that if the body temperature was maintained higher than at this level, death usually ensued.

Rats were anaesthetized as in the hypothermia experiment and placed in a chamber kept at 105° F., with a humidity of 65 per cent., for half-an-hour. Their body temperature rose to 104° F.; they were then removed to a chamber kept at 98° F., with a lower humidity of 40 per cent., for three hours. The body temperature remained at 104° F. They were then left to recover from the anaesthetic at room temperature. Another group of rats was anaesthetized and kept in a constant temperature chamber at 88° F. with a humidity of 30 per cent.; this maintained their body temperature at the normal of 101° F., thus preventing the fall in body temperature of 5° to 10° F., which was found to occur when anaesthetized rats were left at room temperature (78° F.), following nembutal anaesthesia. These rats were kept at this temperature until they fully recovered from their anaesthetic, which lasted for 3 to 4 hours.

It is important in the hyperthermia experiments to anaesthetize the animals at the temperature at which they are to be subjected, since if

subjected to room temperature for a short period of time they tend to drop their body temperature and develop an initial degree of hypothermia.

The unanaesthetized animals were fed in the normal way with water and a standard laboratory " chow ", except for those rats subjected to a temperature of 21° F. and given a special mixture of sustagen and glucose in water, which did not freeze at this temperature.

All the rats were weighed before the experiment started, again following the " stress ", and subsequently for two days thereafter; following this they were weighed at weekly intervals. The consumption of food by the stressed animals was measured and compared with the intake of control groups of rats kept at room temperature (78° F.).

During the experiments, the conscious rats subjected to a temperature of 110° F. for six hours were given water and their normal diet of laboratory " chow ". The average loss of weight was 5 gm. per rat, but the consumption of water had risen from an average of 5 c.c. per six hours to 55 c.c. per six hours. In the hyperthermic rats, there was a weight loss of only 6 gm., despite their inability to drink during the three to four hour period when they were anaesthetized.

As in the previous experiments, the term " heat stress " is used to denote the effect of high temperatures on conscious animals and the effect of hyperthermia on anaesthetized rats. Experiments performed to determine the maximum degree of hyperthermia and " heat stress " to which the rats could be subjected revealed that the unanaesthetized rat was able to withstand a temperature of 110° F. at a humidity of 60 per cent. for six hours. When placed at a temperature of 110° F. for 24 hours, all the rats died in four days with pulmonary disease, although all were alive at the end of the experiment. Rectal temperatures showed a rise of 1° to 2° F. at the end of three hours and 3° to 4° F. at the end of six hours, 40 per cent. of the rats having temperatures up to 105° F. In the anaesthetized rats, the body temperature rose very quickly and when kept at 110° F. for one hour the temperature rose to 106° F., with a 100 per cent. mortality. It was found that if the temperature exceeded 105° F. in the hyperthermic rats, they would not regain consciousness from the anaesthetic. To obtain maximum hyperthermia, with a low mortality, it was necessary to anaesthetize the rats in the heat chamber to prevent the initial hypothermia which occurs when they are anaesthetized at room temperature. They were then left in the chamber at 110° F. for half-an-hour; at the end of this time the body temperature was 104° to 105° F.; the temperature of the chamber was then lowered to 98° F.; this maintains their body temperature at 104° F. The rats were kept at this temperature until they recovered consciousness.

In the " heat-stressed " rats, i.e. the unanaesthetized rats subjected to temperatures of 110° F. for six hours, there were " takes " in 62 per cent.

of the animals following subcutaneous inoculation of 25,000 Walker cells "aged" for 12 hours at room temperature; in a control group, which was not anaesthetized and kept at normal room temperature of 78° F., there were "takes" in 64 per cent. of 47 rats. The hyperthermic anaesthetized rats inoculated with the same cell suspensions sustained "takes" in 100 per cent. of 46 animals (see Table VIII).

TABLE VIII

"TAKES" OF WALKER 256 CARCINOSARCOMA IN RATS FOLLOWING "HYPERTHERMIA" AND "HEAT STRESS"

Type of Stress	*Average rectal temperatures*	*Number of rats*	*% "Takes"*
6 hours at 110° F. Humidity 60%	103° F.	45	62%
Hyperthermia (anaesthetized)	105° F.	46	100%
Controls (unanaesthetized at room temp. 78° F.)	101° F.	47	64%

In the 45 rats which were anaesthetized and kept at their normal body temperature of 101° F. throughout the experiment, there were "takes" in 68 per cent., compared with only 22 per cent. in 22 unanaesthetized control animals kept at their normal room temperature of 78° F.; both groups were inoculated with 25,000 Walker cells "aged" 12 hours (see Table IX).

TABLE IX

"TAKES" OF WALKER 256 CARCINOSARCOMA UNDER NEMBUTAL ANAESTHESIA KEPT AT THEIR NORMAL BODY TEMPERATURE

Type of Stress	*Average rectal temperatures*	*Number of rats*	*% "Takes"*
Normothermia (under anaesthesia)	101° F.	45	68%
Controls (unanaesthetized at room temp. 78° F.)	101° F.	22	22%

Measurement of stress by adreno-cortical response

The adreno-cortical response to the experiments was assessed using the estimation of the total 17-hydroxycorticoids in the plasma, using the technique described by Reddy *et al.* (1956). The blood was obtained at varying times during the "stress" by direct cardiac puncture, without anaesthetic in the unanaesthetized rats. The estimation was carried out on 2 ml. of the rat's plasma, to obtain which 4 to 5 c.c. of blood was necessary. Consequently, it was not possible to use the same rat more than

twice; in fact, the rats usually succumbed after the first cardiac puncture. Three or more rats were bled at the same time to give more accuracy to the sampling and to account for the individual variations from one rat to another. In the "cold stress" experiments the urinary steroids were estimated also and found to be comparable with values obtained from plasma.

An increase in the total plasma 17-hydroxycorticoids was found following cold stress and hypothermia (Fig. 4). In cold stress, the plasma levels returned to normal 48 hours from the beginning of the exposure to cold, but in hypothermia the main response was delayed and was not at its

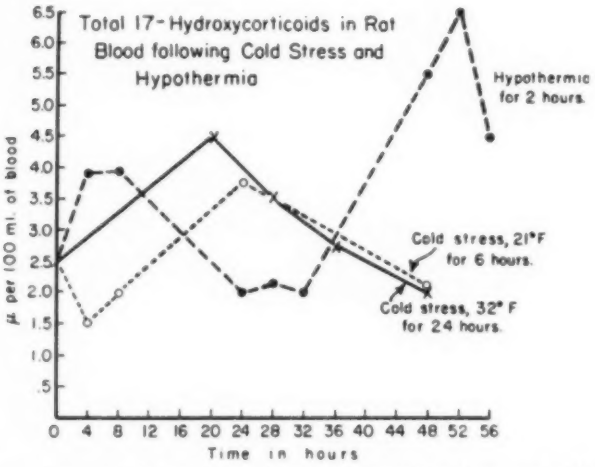


Fig. 4. Adrenocortical response to cold stress and hypothermia as measured by the estimation of the total 17-hydroxycorticoids in the rat's plasma.

height until 48 hours after induction of anaesthesia. This response is similar to that reported by MacPhee and associates (1958) in dogs undergoing hypothermia. The increased adrenocortical activity following cold stress and hypothermia which has been demonstrated is similar to the effect produced on the adrenal cortex by operative stress.

The estimation of the total plasma 17-hydroxycorticoids in both "heat stress" and hyperthermia shows a rise in adrenocortical activity during the first 48 hours following exposure to high temperatures (Fig. 5), but hyperthermia did not show the late rise in the plasma levels demonstrated in hypothermia (Fig. 4).

It has been demonstrated in the above experiments that other forms of physical stress can produce the same type of increased susceptibility to the subcutaneous inoculation of a transmittable tumour in rats. In the first group of rats in which the unanaesthetized animal was subjected to " cold stress " or " heat stress ", it will be noted that in the former there was an increase in the percentage " takes " over the the control group, but in the latter there was no significant difference. The adrenocortical response in both cases, as recorded by the total plasma 17-hydroxycorticoids, shows a stress reaction. Rats undergoing " cold stress " differed from those who were subjected to " heat stress " in that their metabolism was greatly increased, as shown by the increased intake of food required to maintain their body weight during the period of stress. In the second group of rats,

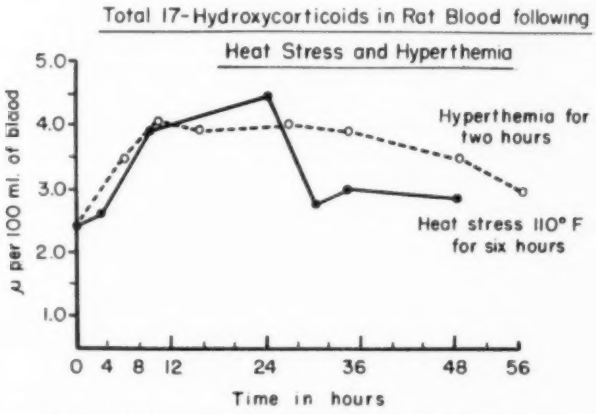


Fig. 5. Adrenocortical response to heat stress and hyperthermia as measured by the estimation of the total 17-hydroxycorticoids in rat's plasma.

which includes those subjected to hypothermia, hyperthermia and normothermia, there is a common factor, namely nembutal anaesthesia; in all these rats there was an increase in the percentage " takes " compared to the " takes " in non-anaesthetized rats kept at room temperature. It has been shown by Travino and associates (1960) that rats anaesthetized and left for two hours at room temperature show an increase in " takes " of Walker tumour injected subcutaneously over non-anaesthetized animals kept under the same conditions. The experiment reported in this paper in which the rats were kept at their normal temperature throughout the period of anaesthesia, demonstrates that although hypo- and hyperthermia probably increase the " stress " reaction, anaesthesia itself can also produce an increased " take " of inoculated Walker cells.

The nature of the physiological mechanism which produces this increased susceptibility (or diminishes the host resistance) to implanted tumour cells must be a central metabolic factor. The difference in the reaction of "cold" and "heat" stress in the percentage "takes" supports the findings of Slawikowski (1960), who showed that the percentage "takes" following coeliotomy in adrenalectomized rats was similar to that following coeliotomy in non-adrenalectomized rats, though somewhat higher in the former (66 per cent. vs. 51 per cent.); the "takes" in the animals having no operation (but an anaesthetic to be consistent with the other two groups) was only 35 per cent. As shown in Table IV the tendency for increased "takes" almost completely disappears when the inoculation of cells is made 48 hours after cold stress. This time element coincides with the fall of the plasma level of the 17-hydroxycorticoids. It may be argued that this physiological reaction is a general response of the body which includes the adrenal glands, but that the essential factor which facilitates the malignant cell to implant is not necessarily the adrenal hormone, although it may play a part. Fisher and Fisher (1959b) have shown that traumatization of the liver is an important factor in the increased growth of tumour in the liver following intraportal injection of Walker tumour. It would appear therefore that any trauma or metabolic disturbance in the normal metabolic processes will create a favourable medium for the growth of the implanted cancer cell, the mechanism of which is as yet unknown.

Effects of starvation and dehydration

The effect of starvation and dehydration on the increased susceptibility to the implantation of Walker tumour in rats has also been investigated. Dietary deficiency in the production of spontaneous tumour has been well described by Tannenbaum and Silverstone (1949). They have demonstrated that the effect of restricted caloric intake and malnutrition in laboratory animals is to diminish the induction and growth of spontaneous and induced tumours. The influence of acute metabolic changes, however, has not previously been investigated in relationship to the increased susceptibility of rats to the inoculation of transmittable malignant tumour cells. In experiments described below the effect of "acute" metabolic changes, such as starvation and dehydration, which can be considered a form of metabolic "stress", have been studied in relationship to the animals' susceptibility to the inoculation of Walker 256 carcinosarcoma. The effect of acute starvation and dehydration is physiologically different from the slower, more chronic effects of the deficiencies produced by feeding animals for long periods of time on diets deficient in certain essential constituents.

Adult female rats, weighing between 215 and 230 gm., were divided into five groups, which were kept under the same conditions and fed with

the same standard laboratory " chow ",* their weights being recorded every other day. On the 24th day four of the groups were subjected to the following experiments: In *Group* 1 the water bottles were removed for 48 hours but the " chow " food was still made available; in *Group* 2 the food was taken away for 48 hours but the water bottles were left; in *Group* 3 the animals were deprived of food and water for 48 hours; *Group* 4 was kept without food for seven days, but water was still available. The *5th Group* was fed and watered in the normal way and used as control animals. A suspension of Walker 256 carcinosarcoma was made, as described previously, and was injected subcutaneously over the abdomens of half of each group at the commencement of the experiment and the other half at the end of the period of deprivation. Control groups of rats were also inoculated at the same time as the experimental groups with the same tumour suspension and the same number of cells. Following the period of deprivation of food and water, the rats were fed the identical diet given before the experiment. Tumours developed in 14–21 days in rats in which " takes " had occurred. The rats in which tumours did not develop were kept for three months to safeguard against the late development of tumours.

Of the 43 rats subjected to dehydration for 48 hours, tumours developed in 77 per cent., and in a control group of 23 rats kept under normal conditions, 60 per cent. developed " takes ". In 75 rats which were subjected to starvation for 48 hours, 89 per cent. developed tumours, and 76 per cent. of the 50 control animals also showed positive " takes ". The combined effect of dehydration and starvation for 48 hours showed 69 per cent. " takes " in 21 rats and 71 per cent. in 21 control animals. Following starvation for seven days in 44 rats, 80 per cent. developed tumours, as compared to 57 per cent. in 42 control rats. There was no mortality in any group during the period of starvation or dehydration.

Weight charts were kept on each group of rats for 24 days before and 10 days after their starvation or dehydration. The average increase in weight was 3 to 5 gm. a day on their normal diet of laboratory " chow ". During starvation for 48 hours, the average loss was 39 gm. per rat, while starvation for 7 days produced an average loss of 50 gm. per rat. Dehydration for 48 hours caused a loss of weight up to 35 gm. per rat, and in a combination of dehydration and starvation for 48 hours, the loss of weight was 35 gm. In the first three groups the rats' weights returned to the pre-experimental level in 48 hours, and in the fourth group within four days. It is interesting to note that the rats which had suffered starvation for seven days had gained 30 gm. over their pre-starvation

* The food used in our laboratory was the " Purina " Lab. Chow. (Constituents of " Purina " Lab. Chow, as supplied by the manufacturers : crude protein, not less than 23 per cent.; crude fats, not less than 5.0 per cent.; crude fibre, not more than 6.0 per cent.; N.F.E., not less than 44 per cent.)

weight seven days after the end of their period of starvation, whereas the control rats over the same period had maintained a steady weight.

The effect of starvation and dehydration on the experimental rats is to produce a disturbance in the metabolism of the body, which may be considered a metabolic " stress ". Anabolism is replaced by katabolism and there is a mobilization of the body's reserves. In the experiment described above it is interesting to note that the influence of starvation or dehydration, and the combination of both, does not produce an increase in the susceptibility of the animal to the subcutaneous inoculation of Walker tumour, but following extreme starvation for a period of seven days, when there has been a loss of one fifth of their body weight, there is an increase in the percentage " takes " over a normal control group. This would lead us to believe that, following a marked katabolic stress, the conditions in the tissues of the experimental animal are more favourable to the implanted malignant cell than in the normal healthy animal.

Tannenbaum and Silverstone (1949) have shown that malnutrition tends to diminish the incidence of the formation of skin tumours and hepatomas in mice, but they have failed to inhibit the formation of mammary carcinoma in mice by intermittent fasting. There is no contraindication between the influences of malnutrition shown by this investigation and the data presented in the above experiments, as the nature of the physiological response would differ in " acute " starvation from that of chronic malnutrition, as the " takes " following inoculation of Walker carcinosarcoma indicate the susceptibility or " host resistance " to the implantation of the cancer rather than the rate of growth of a spontaneous tumour.

Schneewind (1958) has recently stressed the importance of the nutritional state of patients in the pre-operative period in relationship to the operative and post-operative complications which may ensue. He emphasizes the importance of the patient gaining weight during the immediate pre-operative period, i.e. the patient should be in an anabolic rather than a katabolic state. This may be of even greater importance in patients with malignant disease, especially in patients with carcinoma of the alimentary canal, where there has been a state of " acute " starvation due to intestinal obstruction, if the conditions which have been shown to occur in the experimental animal are true in the human. Animal experiments and clinical observation tend to support the evidence put forward by Buinauskas *et al.* (1958) that operative stress increases the susceptibility of rats to the " takes " of Walker tumour. Any further stress, such as starvation in a pre-operative patient, would increase the " stress " of the surgical procedure and would theoretically diminish the host resistance to the implantation of the disseminating cancer cells and the consequent development of metastasis.

It will therefore be seen in the experiments described that " stress " produced in rats by operative or other means increases the susceptibility of the animal to the implanted malignant cell or, if considered in another way, the stress reaction diminishes the host resistance. What, if any, relationship has this finding in the patient undergoing surgical operation for malignant disease? In the majority of surgical cases with neoplastic disease there is no definite evidence of there being any interference with host resistance, but most surgeons can remember cases in which, following operation, there has been a rapid dissemination of the neoplasm, with widespread appearance of fast-growing secondaries. There is a risk in any operative procedure of spread of malignant cells by direct overflow into the wound, associated with the risk of blood-borne carriage of cells to other organs. Also there is the " katabolic " stress of the operation, which tends to diminish in the post-operative phase the resistance of the tissue to the implantation and growth of the malignant cell.

Factors controlling the development of metastasis

Dissemination of cancer cells during operation is inevitable in most cases of surgery for malignant disease. The body, however, has a resistance to the neoplastic cells and it is conceivable that, as in many infectious processes, the determining factors are the virulence of the neoplasm and the volume of dissemination which occurs.

Fisher *et al.* (1959a) have demonstrated that the development of hepatic metastases in rats, following direct injection of Walker 256 carcinosarcoma cells into the portal vein, is dependent on the number of tumour cells introduced. In discussing the ability of tumour cells to metastasize in mice, Watanabe (1954) postulates that the single cells circulating in the blood stream are of no significance, but that the clumps of tumour cells which enter the blood stream by invasion of the veins are responsible for the development of distant metastasis. Ziedman *et al.* (1950) draw attention to the importance of the presence of the primary on the development and growth of secondary metastasis. Although it has been well recognized that in some cases of neoplastic disease the secondaries become inactive after the removal of the primary, the exact nature of this inhibition has not yet been demonstrated. Evidence presented by Schatten *et al.* (1958) shows that a primary tumour of sufficient size will inhibit the growth of distant metastasis and he argues that secondaries are established before the primary tumour has become large. This is contrary to the general experience of most surgeons.

The characteristics of the cancer cell itself play a part in its own dissemination, and it is likely that in the near future various neoplastic cells will be shown to possess varying invasive and selective characters similar to those of bacterial organisms. Both animal experiments (Lucke *et al.*, 1952) and clinical observation show that some tissues in the body are more

susceptible to the formation of secondaries than others. Haddow (1934) postulated that in the liver there is a specific mechanism involved and this is the source of a growth-promoting substance of paramount importance in the division of both normal and malignant cells. Further evidence of this is seen in the experimental work of Fisher and Fisher (1959b), in which they show a great number of metastases occurring in the liver following injury during laparotomy. This re-emphasizes the metabolic factors which control the initial implantation of the malignant cell. Much of the work in recent years on the endocrine dependency of tumours indicates that the anabolic or katabolic activity of the malignant cell in the tissues is governed by the hormonal balance of the host.

The effect of surgical operation on these factors may, in certain cases, enhance the development of an environment favourable to the implantation and growth of the neoplastic cell, which has been shown by Wiseman and Ghadially (1958) to be able to assimilate the essential amino acids more readily than normal cells. If animal experiments can be used as an indication for the human subject, then it will be seen from the experiments already described that any " katabolic " phase, such as " acute " starvation or operative stress, has an influence on the resistance of the patient to the cancer cell.

The immunological reaction of the body to neoplastic cells is one of great importance and is at the present time being investigated in many centres. The effect of the antibody reaction on the disseminating cell may be the vital factor determining its viability.

The dormancy of the cancer cell has been mentioned previously, and Hadfield (1954), in the Kettle lecture at this College, put forward the hypothesis that anorexia of the scar tissue is one of the factors which inhibits the development of metastasis, and, consequently, any factor which increases the vascularity of the area, such as infection or trauma, will produce re-activation of the cell and the development of a secondary metastasis after many years of inactivity. This is often demonstrated during palliative operations on cancer patients in whom growth is known to have been left at the time of surgery. In the post-operative period, a severe local infection may occur with subsequent formation of fibrous tissue, and consequent slow dormancy or growth of the neoplasm.

From the animal experiments described in this lecture, factors which may control the development of metastasis during surgical operation can be summarized as follows:

(1) Any procedure which tends to disseminate malignant cells

This will include the unnecessary handling of the neoplasm and procedures which encourage the release of cancer cells, such as incision of the growth or contamination of healthy tissue with exudates or blood from the affected organ.

(2) Forms of stress such as surgical shock

It has been clearly demonstrated in animals that any form of stress will tend to increase the susceptibility of the tissues to the implantation of malignant cells. From this it may be concluded that in the human patient similar stress plays some part in the development of secondary growth.

(3) Starvation

Any metabolic disturbance which can be considered katabolic may enhance the development of metastasis in the tissues. This may be of importance during the post-operative phase of any surgical procedure and the aim of post-operative management should be restore an anabolic metabolism as soon as possible.

Measures to limit the dissemination of cancer cells at operation

In 1907, Ryall described the importance of the dissemination of cancer cel s at operation. He coined the term " cancer infection ", comparing the cancer cell with bacteria, and showed conclusively that the neoplastic cell should be treated with the same stringent aseptic techniques as those generally used against micro-organisms. He stressed that the only difference between septic and cancer infection is that the former manifests itself early, whereas the latter shows itself late, after all is thought to be well. With such advances in surgical technique as have been made during the last sixty years, it would be well to re-affirm the principles which Ryall laid down for operative procedures in cancer. It was he who emphasized the error of incision into the cancerous tumour at operation, of piecemeal removal of the growth, of curettage, and, above all, he pointed out the dissemination that could occur at operation either by rough manipulation of the tumour or by rupture of affected lymph nodes and vessels.

These principles have been re-emphasized in recent years by Naunton Morgan, Lloyd-Davies and many others in this country, and by Cole and his associates in America. The concept of the infectivity of the malignant cell led to the introduction of chemotherapy in cancer operations. The results in operations for carcinoma of the colon and rectum, using mercury perchloride, have already been discussed in this lecture. The early reports of the use of nitrogen mustard as a prophylactic and adjuvant in surgical treatment of cancer has been reported by Mrazek *et al.* (1959). Although there is general agreement that there is as yet no satisfactory anti-cancer drug, nitrogen mustard used locally during operation, and intravenously in the immediate post-operative period, has extended the possible cure rate of malignant disease in some patients. However, it will be some years before it is possible to assess fully the results of this therapy.

Blood-borne dissemination during the time of operation can, in many organs, be controlled by early ligature of the vessels, preferably before manipulation and mobilization of the tumour.

Limitation of the " stress " of operation

Work which is still in progress indicates that the thyroid gland may play a very important part in the " stress " reaction and its effect on the implanting cancer cell. There is strong evidence to suggest that rats given propyl thiouracil for some time before being subjected to " stress " do not show the same increased susceptibility to the implanted cancer cell as previously demonstrated in this lecture.

Humphrey *et al.* (1959) have shown that there is no difference in the " takes " of Walker tumour in hyper-, hypo-, and eu-thyroid states. It can be argued that the production of a hypothyroid state may block the increased susceptibility to implanted Walker tumour shown to occur in rats following cold " stress ". The method by which the host resistance has been increased is difficult to determine. The general metabolic response of the body would be diminished by the administration of propyl thiouracil, thus possibly depriving the cancer cell of the necessary nutrition during critical stages of its implantation. This is in contradistinction to the increased metabolic states which occur following operative and cold " stress " in normal rats. Humphrey *et al.* (1960) have shown that nitrogen mustard is much more effective in hypothyroid than hyper- or euthyroid rats. This may be due to a decrease in " stress " which occurs after administration of the drug (Schneewind *et al.*, 1958), thus potentiating its cytotoxic properties. Humphrey has also demonstrated that there is no diminution in the toxicity of the nitrogen mustard in the hypothyroid animal, but a diminished percentage " take " when compared with the euthyroid and hyperthyroid rats.

Much of the work reported in this lecture has, by necessity, been on animal experiments using tumours artificially produced. To what extent the results are valid in the human subject must be left to conjecture. But it is worth noting that John Hunter performed animal experiments which have proved of great benefit in recent years in the field of plastic surgery. It was he who performed the first graft by transplanting a cock's spur into its comb and showing that it continued to grow. He also performed experiments on animals to demonstrate the method and factors controlling bone growth.

It remains for us to apply the general principles of what we can learn from animal experiments in the practice of our surgical treatment of patients suffering from malignant disease. Paget wrote in 1889: " All reasoning from statistics is liable to many errors. The eruption of the specific fevers and of syphilis, the inflammation of typhoid, the lesions of tuberculosis, all show dependence of the seed upon the soil. The best work in the pathology of cancer is now done by those who are studying the nature of the seed. They are like scientific botanists, and he who turns over the records of cases of cancer is only a ploughman, but his observations of the properties of the soil may also be useful."

Those who practise surgery are still " ploughmen " and our observations on the " soil " are still of great importance.

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HONOURS CONFERRED ON FELLOWS AND MEMBERS

In the Birthday Honours List, H.M. The Queen graciously conferred the following Honours on Fellows and Members of the College:

K.B.E. (Military Division)	AIR VICE-MARSHAL C. A. RUMBALL, C.B.E., M.R.C.S., Honorary Physician to The Queen
Knighthood	W. E. CHIESMAN, C.B., M.R.C.S. J. S. RICHARDSON, M.V.O., M.R.C.S. G. D. ROBB, C.M.G., F.R.C.S. B. W. RYCROFT, O.B.E., F.R.C.S.
C.B. (Military Division)	SURGEON VICE-ADMIRAL W. R. S. PANCKRIDGE, M.R.C.S., Honorary Physician to The Queen
C.B. (Civil Division)	L. J. CLAPHAM, M.R.C.S. PROFESSOR M. A. RUSHTON, F.D.S.R.C.S., Dean of the Faculty of Dental Surgery
M.V.O.	WING COMMANDER H. B. KELLY, M.R.C.S.
O.B.E. (Military Division)	SURGEON COMMANDER C. V. HARRIES, R.N., M.R.C.S. WING COMMANDER J. E. MALCOLM, F.R.C.S.
O.B.E. (Civil Division)	H. R. J. DONALD, M.R.C.S. G. D. GORDON, M.R.C.S. R. F. H. HINRICHSEN, F.R.C.S.
M.B.E. (Civil Division)	E. H. WILLIAMS, M.R.C.S.

STATISTICS IN MEDICINE*

by

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The scope of statistics

I start with two quotations to illustrate two different views of statistics:

(1) " [Statistical proof], to me at least, is the dullest and most unreliable way of establishing biological facts. . . . If surgeons would become scientists again instead of statisticians, the problems could be resolved." (Osborn, 1959.)

(2) " Statistics have got to be used in nearly all clinical research, and it is better that they should be good statistics than bad. There is no need for the research worker in clinical medicine to have a knowledge of statistics, but it is an enormous advantage if he has, even though his knowledge of this subject is not very profound." (Atkins, 1958.)

These two quotations represent points of view which are fairly widely held, and it will be fairly clear that I am myself more sympathetic to one view rather than the other. I believe, though, that a good deal of difficulty is caused by misunderstandings of one sort or another. It is not always clear, in these disputes, in what sense the word " statistics " is being used.

My main purpose in this paper is to try to explain what I understand by the subject of statistics, what sort of problems it can deal with, what difficulties are likely to arise. It will clearly be impossible to discuss in detail any but the simplest techniques for handling data. I shall be content if I can sketch the background sufficiently for you to fill in the details from one of the many elementary books on the subject. Four books worth mentioning are: Bradford Hill's *Principles of medical statistics*, Moroney's *Facts from figures*, Bailey's *Statistical methods in biology* and Finney's *Experimental design and its statistical basis*.

According to the *Oxford Dictionary* " statistics " originally meant " that branch of political science dealing with the collection, classification, and discussion of facts bearing on the condition of a state or community. In recent use, the department of study that has for its object the collection and arrangement of numerical facts or data, whether relating to human

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* This paper is a shortened version of three lectures given as part of a Course on Genetics, Statistics and Radio-isotopes at the Institute of Basic Medical Sciences, London, in October 1959.

affairs or natural phenomena". Apart from the apparent identification of human affairs with unnatural phenomena, this is a satisfactory definition; and a revealing one, too, because it indicates the way in which useful facts about a human community can hardly avoid being numerical. It was a long time before accurate numerical data were available for the whole country, but the celebrated "bills of mortality" which John Graunt analysed in the 17th century provided a very effective description of mortality in a smaller community—the City of London.

We are all familiar nowadays with this use of statistical data to describe general features of large populations. The Registrar General's routine compilations of births and deaths, the decennial census, indices representing the general level of prices or productivity, estimates of audiences for television programmes—all these and many more suggest that numerical data are essential, in a purely descriptive way, to help us to know what a community is like and how it behaves.

There are two points I want to emphasize about this sort of statistics. The first is that their collection and interpretation do not usually present any mathematical difficulties, but they do usually require an intimate knowledge of the field of study. If you wish to make any use of the mortality statistics for a particular disease over a period of time, you need to know how the Registrar-General defines that cause of death, what the convention is about multiple causes of death, whether there have been any changes from year to year in the categories included, whether standards of diagnosis have improved, and so on. Many of the social statistics quoted in the press and on the public platform are complicated things and are liable to be misunderstood by the layman.

The second point is that we are so used to this bombardment of figures that we are inclined to overlook a rather remarkable thing—that each is based on individual observations which are themselves very irregular and unpredictable. Large aggregates of observations very often present regularities and patterns which cannot possibly be discerned in single observations. The annual statistics of mortality from cancer of the lung, for example, reveal trends which would not be shown by observing that a patient of a certain age, sex, social status died of that disease whereas his next-door neighbour did not. In the same way a particular road accident may seem to the victim's family to occur quite haphazardly, but a study of accident statistics for the whole country will be revealing in many ways. Insurance companies could not stay in business if this property of the predictable behaviour of large populations were not true. It is, of course, an essential feature of modern physics. Individual molecules, atoms and sub-atomic particles apparently behave in anything but a disciplined way, and yet aggregates of these particles follow recognizable laws of behaviour.

TABLE I

FREQUENCY DISTRIBUTION, CONTINUOUS MEASUREMENT

Age distribution of 1,357 male patients with lung cancer

Age	*Frequency (No. of patients)*
25–	17
35–	116
45–	493
55–	545
65–74	186
	1,357

TABLE II

FREQUENCY DISTRIBUTION, DISCONTINUOUS MEASUREMENT (GROUPED)

Frequency of different numbers of lesions caused by smallpox virus in egg membranes

No. of lesions	*Frequency (No. of membranes)*
0–	1
10–	6
20–	14
30–	14
40–	17
50–	8
60–	9
70–	3
80–	6
90–	1
100–	0
110–119	1
	80

TABLE III

FREQUENCY DISTRIBUTION, DISCONTINUOUS VARIABLE (UNGROUPED)

Frequencies of different numbers of males in sibships of eight children

No. of Males	*Frequency (No. of sibships)*
0	161
1	1,152
2	3,951
3	7,603
4	10,263
5	8,498
6	4,948
7	1,655
8	264
	38,495

Up to about 1900 statistics was concerned largely with the problems of collecting data about populations, and using them for descriptive purposes. During the present century the scope has widened in various directions, and one of the consequences is that statistical methods are frequently applied to small numbers of experimental observations. At first sight a problem involving, say, six determinations of the concentration of a particular protein in a patient's blood does not seem to bear much relationship to these large population studies I have been mentioning. The connection is there, however. Almost any measurement is subject to random, unpredictable variation. We hardly ever get the same answer twice. Repeated observations, therefore, show much the same properties as the individual members of a large population. If we could go on long enough we could make accurate statements about the whole collection of observations, but unfortunately our observations are often only too few. So the problem is to know what can be said about the long-term behaviour of a series of observations on the basis of a relatively small selection of individual readings. This is sometimes called the problem of " statistical inference ", and I shall be discussing it in some detail in the next section.

For the rest of this section I want to stick to the 19th century, and discuss some of the language which statisticians use in describing and summarizing collections of data.

If you have a large collection of measurements in a more or less haphazard order, it is very difficult to size them up. One of the most useful methods of evoking some sort of order is to construct a *frequency distribution*. To do this the scale of the measurement (or *variable*, as it is often called) is divided into a number of different groups, and a count is made of how many observations fall into each group; this is called the *frequency* for that group. Table I shows a frequency distribution for a continuous measurement—age. In Table II the measurement is discontinuous—in fact it must be a whole number. Sometimes, when the variable is discontinuous and there are not many possible values, there is no need to form groups (Table III).

Frequency distributions may be depicted visually by *histograms*, which are diagrams in which the frequency is shown vertically and the measurement horizontally (Figs. 1, 2 and 3). For grouped measurements with groups of equal extent the frequency is shown as the height of a block whose width corresponds to the group. For ungrouped measurements the frequency may be shown as the height of a vertical line drawn at the appropriate point on the scale.

The presentation of a frequency distribution, either by a table or visually by a histogram, immediately helps to summarize the data. That is, it gives you a good idea " what the data look like ". However, we usually wish to go beyond this and concentrate on one or two special features of

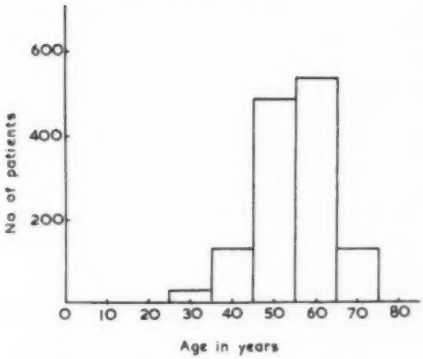

Fig. 1. Histogram for data in Table I.

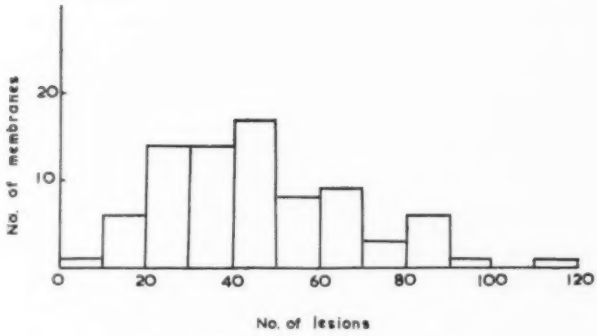

Fig. 2. Histogram for data in Table II.

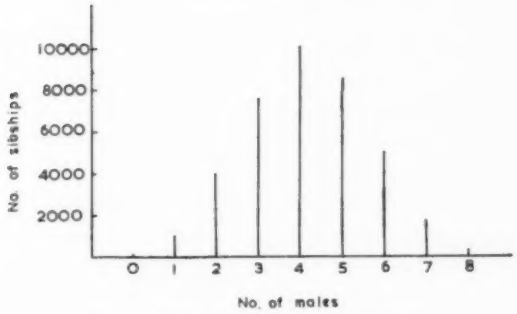

Fig. 3. Histogram for data in Table III.

the distribution. The most important special feature is the *average*, or more precisely the *arithmetic mean*, or just simply the *mean*. There is no need to explain what this is, but I want here to mention the notation which is often used to denote the mean. Statisticians frequently use a letter like x or y to denote a particular sort of measurement, like height, or blood sugar concentration and so on. The symbol x does not refer to a definite fixed value, but represents any observed value of the measurement. Suppose we have n values of x. The usual notation for the mean of these n values is $\bar{x}$, and the notation for the way it is calculated is

$$\bar{x} = \frac{\Sigma x}{n}.$$

Note that Σ does not indicate a number but an operation. It means " the sum of ". Occasionally the letter S might be used. Either of these is called the *summation sign*.

It is perhaps worth mentioning that occasionally some types of averages other than the arithmetic mean are used. In bacteriological and serological work one frequently encounters the *geometric mean*. The point is that, for this sort of work, serial dilutions are frequently used, so the dilution factors may be a series like 2, 4, 8, 16, 32, 64, etc. Now, if you have a series of titres expressed on this scale of dilutions, the logarithms of the possible titres will be equally spaced, and it seems more natural to work with these logarithms than with the very unevenly spaced dilutions. If we take the arithmetic mean of the logarithms and change this back to the original scale of dilutions we get the geometric mean of the original dilutions. For example, if there were two titres of 4 and 16, the arithmetic mean would be 10, but the geometric mean would be 8.

The next step after calculating a mean is to give some idea of the degree of variation about that mean. There are innumerable ways of doing this. One fairly appealing way would be to ask by how much, on the average, the individual values differ from the mean. This is fairly easy to do, although not as easy as you might think when there are a large number of observations. Unfortunately, it is mathematically unsatisfactory for various reasons. It turns out to be better to calculate the average of the squares of the differences from the mean. This quantity is called the *variance*, and its formula is:

$$\frac{\Sigma(x - \bar{x})^2}{n}.$$

This formula is the version usually given in the older books on statistics, but during the last 40 or 50 years it has been realized that it is mathematically more satisfactory to use the slightly different formula:

$$s^2 = \frac{\Sigma(x - \bar{x})^2}{n - 1}.$$

(The difference between the two formulae is obviously rather trivial when n is large.) Sometimes the variance is denoted by σ^2.

Now, the variance is based on squares of differences $x - \bar{x}$, and the units of the variance will be the square of the units of x. If x is in inches, s^2 will be in square inches. It is rather convenient to have a measure of variation in the same units as the original readings, and so we can take the square root of the variance, which is called the *standard deviation:*

$$s = \sqrt{\left(\frac{\Sigma (x - \bar{x})^2}{n - 1}\right)}.$$

One has an intuitive grasp of what the arithmetic mean of a series of readings implies and it is not too difficult to make an intelligent guess at its value without doing any calculation. But what interpretation do we put on the standard deviation? A rough guide is that for most collections of readings, something like 95 per cent. of the observations will lie between the limits:

(Mean + 2 standard deviations)
and (Mean − 2 standard deviations).

That is, a range of 4 standard deviations should cover pretty well all the readings. If there are not many observations, the difference between the biggest and the least is likely to be about 3 standard deviations.

In the upper half of Table IV I have illustrated the calculation of the standard deviation for a group of 7 readings. One would usually regard 7 as too small a number of observations to give an accurate idea of variability, but it is rather easier to show the steps involved with a small number like that. Notice that the readings are not grouped into a frequency distribution; if one did that the frequencies would be ridiculously small. With larger numbers of observations one could group, and the calculations would then take a rather different form. It is probably better, if at all possible, to calculate the mean and standard deviation from the ungrouped observations, using the frequency distribution merely as a general summary of the whole series.

With a small number of observations the calculations for the standard deviation look perhaps a little irritating but not too troublesome. It is, however, quite a nuisance to have to subtract the mean from every reading, particularly when, as in the example of Table IV, the mean does not come out to a whole number. Furthermore, in writing down all these differences it is quite easy to make a mistake. It is usually found much more satisfactory to use an alternative formula for $\Sigma(x - \bar{x})^2$, the *sum of squares about the mean.* This is:

$$\Sigma(x - \bar{x})^2 = \Sigma x^2 - (\Sigma x)^2/n.$$

Note the distinction between Σx^2 and $(\Sigma x)^2$. The calculations are given in the lower half of Table IV, and you will see that they give the same answer for $\Sigma(x - \bar{x})^2$. After that the calculation proceeds as before.

As a check on the calculations, the *range* (difference between the highest and the lowest observations) is 7.2 − 3.6 = 3.6, which is 2.72 times the standard deviation.

TABLE IV

CALCULATION OF STANDARD DEVIATION

$n = 7$

Direct method

x	$x-\bar{x}$	$(x-\bar{x})^2$	
4.7	−0.914	0.8354	$s^2 = \frac{10.5086}{6}$
3.6	−2.014	4.0562	
7.2	1.586	2.5154	
7.1	1.486	2.2082	
5.4	−0.214	0.0458	$= 1.7514$
6.3	0.686	0.4706	
5.0	−0.614	0.3770	$s = 1.323$
$\Sigma x = 39.3$		$\Sigma(x-\bar{x})^2 = 10.5086$	

$\bar{x} = 39.3/7 = 5.614$

Alternative method for $\Sigma(x-\bar{x})^2$

x	x^2	
4.7	22.09	$\Sigma(x-\bar{x})^2 = \Sigma x^2 - \frac{(\Sigma x)^2}{n}$
3.6	12.96	
7.2	51.84	
7.1	50.41	
5.4	29.16	$= 231.15 - \frac{(39.3)^2}{7}$
6.3	39.69	
5.0	25.00	$= 231.15 - 220.6414$
$\Sigma x = 39.3$	$\Sigma x^2 = 231.15$	$= 10.5086$

The methods of statistics

In the last section I wrote that modern statistical methods are largely concerned with the problem of statistical inference. If there is an aggregate, or population, of individual measurements which vary in an unpredictable or (as we usually say) *random* way, what can we say about the whole collection on the basis of a limited selection from them? This is sometimes called the *sampling problem*, and a familiar example is provided by the public opinion poll. There is a definite population—the electorate of the country—and one wishes to know some particular characteristic of this population—say, the proportion of people who at the moment of sampling intend to vote for a particular party. It is not practicable to interview the whole population, and so a sample is chosen and interviewed. The problem then is to know how accurate the sample results are as an indication of the results for the whole population. There are, of course, many other problems concerned with opinion polls—whether the sample is a biased one, whether the answers given by the people interviewed are true, and so on—but these do not concern us here.

Another example of sampling from a definite population was provided by the Registrar General at the last census. He took a 1 per cent. sample of his returns and published the results on these relatively early so as to provide a reasonably good guide to the exact results some years before these exact results would be ready. This sample was what is called a *random sample*, that is each household had an equal chance of being included. Opinion polls are not done in quite this way and one consequence is that it is difficult to know theoretically exactly how accurate they are.

Now let us consider a rather different situation. If we toss a penny over and over again we get a series of heads and tails which vary in an entirely unpredictable way. If we went on indefinitely we could collect a very large number of results, and the proportion of heads would be a physical characteristic of the coin analogous to its weight or its volume. This long-run proportion of heads is called the *probability* of getting heads. Suppose this probability for a particular coin is, say, 0.498 (it will presumably be near 0.5 in a normal penny). Then if we toss the penny 10 times we shall not get exactly 49.8 per cent. of heads (obviously, because we can't get 4.98 heads). The number of heads, in fact, might quite easily be 4, 5 or 6 or even further away from the average of about 5. The question then arises, in n tosses, how far is the proportion of heads likely to differ from the long-run proportion. If we find, say, r heads out of n, what can we say about the long-run proportion—is it fairly certain that the long-run proportion is greater than $\frac{1}{2}$, for instance? If we found 58 heads out of 100 there would be no particular reason to suspect the penny of being biased; if we found 88 we should know there was something wrong with it. But what about, say, 68?

The problem I want to emphasize here is that the mathematical problem of determining what we can say about a *hypothetical* long-run series on the basis of an observed short run is just the same as that of describing an *actual* large population on the basis of a small sample.

Let us consider now an example rather more relevant to medical research. Suppose we have a particular technique for estimating γ-globulin concentrations, and we know that it has a certain experimental error. We take 5 readings for a particular serum, and discover that they vary to some extent. What can we say about the correct value? (I am assuming here that the method is unbiased, in the sense that in the long-run it would give the correct value on the average.)

If we were able to do a very large number of determinations they could be arranged in a frequency distribution, and they would have a certain mean and standard deviation, say m and σ. (To give an idea of the shape of the distribution we can ignore any grouping and draw the histogram as a smooth curve.) Now suppose we take n readings, and let us think of

this as a random sample from the whole distribution. The mean of these n readings, $\bar{x}$, will not be exactly the same as m; it will sometimes be greater and sometimes less. In fact, if we imagined doing this procedure over and over again, and taking note of all the different values of $\bar{x}$, we should find that they followed a distribution centred around m, but with a much smaller scatter. What can we say about this distribution? In the first place, it will be very near in shape to a particular sort of distribution called a *normal distribution*. This is shaped rather like a bell, and is symmetrical. Secondly, the variability of $\bar{x}$ will depend on (i) the variability of the original readings, x, which is measured by the standard deviation, σ; and (ii) the size of the sample, n. In fact, the standard deviation of $\bar{x}$ is $\sigma / \sqrt{n}$, and is called the *standard error* of the mean. So we can write

$$\text{S.E.}(\bar{x}) = \sigma / \sqrt{n}.$$

Now, one of the properties of the normal distribution is that only about 5 per cent. of the observations lie outside limits placed at twice the standard deviation on either side of the mean. So we can say that it is rather unlikely (i.e. it will only happen once in 20 times) that a particular value of $\bar{x}$ differs from the correct mean m by more than $2\sigma / \sqrt{n}$. There are two main ways in which this result is used:

(1) *In a significance test:* suppose there is some theory or hypothesis that the mean for a particular serum is a value M. We know that if this were true, the mean of a sample of n readings would be unlikely to lie outside the limits $M \pm 2\sigma / \sqrt{n}$. So let us see whether our observed value does lie outside these limits. If it is greater than $M + 2\sigma / \sqrt{n}$, this will suggest that the true value is greater than M, and we say that $\bar{x}$ is significantly greater than M at the 5 per cent. level. If it is less than $M - 2\sigma / \sqrt{n}$, this will suggest that the true value is less than M, and we say that $\bar{x}$ is significantly less than M at the 5 per cent. level.

(2) *To give confidence limits.* We can be pretty sure that $\bar{x}$ does not differ from M by more than $2\sigma / \sqrt{n}$. So if we calculate limits

$$\bar{x} \pm 2\sigma / \sqrt{n}$$

on either side of our observed value we shall be pretty sure that this range includes the true value M. These limits are called 95 per cent. confidence limits.

I am afraid that I have had to describe these concepts too rapidly for anyone meeting them for the first time to be entirely at home with them. More leisurely descriptions will be found in the elementary books which I have mentioned. There are two developments of these results which should be mentioned at this stage. In most problems in which we have a

collection of n readings we do not know σ, the standard deviation in the whole population. What we can do is to use, as an estimate of σ, the standard deviation s in the sample; the calculation of this is illustrated in Table IV. If we do this, it turns out that the factor 2 by which the standard error was previously multiplied has to be replaced by a rather bigger factor, depending on the size of n. These factors are obtained from tables of the t-distribution, and again I shall have to refer you to books for the details.

Secondly, we very often wish to compare two or more groups of readings. If we have n readings from one serum and n from another, the means will probably differ, but how certain can we be that this difference is not due to the inevitable sampling variation to which each mean is subject? Again, I shall have to refer you to the books.

I am, however, going to consider the problem of comparing two groups, but in a rather simpler case where the readings are qualitative, like heads and tails, rather than measurements. Table V shows the results of a clinical trial to compare the incidence of thrombophlebitis in using rubber infusion sets, as compared with a newer type of plastic equipment. On the face of it, it appears that the plastic sets are preferable, but can we be reasonably certain that this sort of difference would not have arisen purely by chance? To put this another way, suppose that in fact the two sets were equally likely to give rise to thrombophlebitis, is it likely that the results in two samples of this size would differ by as much as they did in

TABLE V

RESULTS OF A TRIAL TO COMPARE THE INCIDENCE OF THROMBOPHLEBITIS FOLLOWING INFUSION WITH PLASTIC AND RED RUBBER GIVING-SETS.

Calculations of χ^2

Observed frequencies

	Throm.	*No throm.*	*Total*
Plastic	57	123	180
Rubber	105	84	189
TOTAL	162	207	369

Expected frequencies

		Total
79.02	100.98	180.00
82.98	106.02	189.00
162.00	207.00	369.00

Discrepancies, O–E

		Total
–22.02	22.02	0
22.02	–22.02	0
0	0	0

$$\chi^2 = \frac{(22.02)^2}{79.02} + \frac{(22.02)^2}{100.98} + \frac{(22.02)^2}{82.98} + \frac{(22.02)^2}{106.02}$$

$$= 6.136 + 4.802 + 5.843 + 4.573$$

$$= 21.35$$

this trial? What we need, then, is a significance test of what is called the *null hypothesis* that there is no real difference between the sets in the incidence of thrombophlebitis.

The results, as I have shown them in Table V, are arranged in what is often called a 2 × 2 table. The marginal totals show the total numbers of subjects in the two groups, and the total numbers with and without thrombophlebitis. Now, if the null hypothesis were true we could write down the numbers which we should expect in the four cells inside the table. For example, the number of subjects with thrombophlebitis with the plastic set would be expected to be

$$\frac{162}{369} \times 180 = 79.02.$$

The expected numbers are shown in Table V and it is fairly clear that the bigger the difference between the results for the two sets, the bigger the discrepancy between the observed and expected numbers. These discrepancies (which we can write as O–E) are shown in Table V, and are the same apart from their sign.

How big can we expect these discrepancies to be purely by chance? The answer is given by the χ^2 (chi-squared) test. We calculate

$$\chi^2 = \sum \left(\frac{(O-E)^2}{E} \right)$$

adding over the four cells in the table. The calculations in our example are given in Table V, and show that $\chi^2 = 21.35$. If the null hypothesis were true the value of χ^2 would vary to some extent, but its distribution can be obtained mathematically. This is called the χ^2-distribution with 1 degree of freedom, and details are given in most of the books. It is known, for example, that only once in 20 times will the value of χ^2 exceed 3.84, and only once in 1,000 times will it exceed 10.83. This is, of course, assuming the null hypothesis to be true. Now, our value is 21.35, and would be very unlikely indeed to arise on the null hypothesis. We should therefore feel quite confident in rejecting this null hypothesis and accepting the difference as a real one.

One of the questions most frequently put to a statistician is: "How many observations are needed?" It is not by any means an easy question to answer. The answer depends on what you want to achieve by the investigation—how accurately you wish to determine an average, how easily you wish to detect a difference of a certain size. Consider the simple question of estimating the mean of several observations. We have seen that the precision with which we can measure the mean of n readings depends (*a*) on how big n is; and (*b*) on the variability of the individual readings. If we know this basic variability, then we can easily work out

how many observations are needed for a given degree of precision. Often, perhaps usually, this variability is unknown, and the only answer then is to take some observations, make an estimate of the variability and then work out how many more observations are needed.

The pitfalls of statistics

The classical fallacy in statistics is what is called the "nonsense" correlation. If we take the annual imports of tobacco in successive years from, say, 1870 and correlate them with the number of divorces made absolute in the corresponding years, the relationship is a very close one. But it would be as misleading to claim that tobacco is a serious cause of marital distress as it is to claim that the breakdown of marriage causes people to take up smoking. Clearly, the direct causative relationship between these two factors is negligible. Both measurements have increased steadily with time, and it is not surprising that there is a close association between them.

The moral of this, then, is that statistical association does not imply causation. One of the main difficulties of interpreting relationships and comparisons arising from uncontrolled data is to decide whether the superficial explanation, if any, is the correct one. Let us consider a problem of comparison which arises very frequently in vital statistics. The annual death rate in 1950 for England and Wales was 11.6 per 1,000 population; for Puerto Rico in the same year it was 9.9 per 1,000, about 15 per cent. less than for England and Wales. Can we say, without danger of misleading anyone, that mortality was, in 1950, higher in England and Wales than in Puerto Rico. Certainly not! If you look at the death rates separately for each age group, you find that in Puerto Rico the rates were two or three times as high as in England and Wales up to age 45, and that the rates are rather similar in middle age, being perhaps somewhat lower at old ages. The England and Wales rates are better at all ages up to about 60. The reason for the apparent paradox is that in Puerto Rico the population is on the average much younger than here. For example, about 53 per cent. of the population is less than 20 years of age, as compared with 28 per cent. in this country. The crude death rate for the whole country (which is just total deaths divided by total population) therefore is influenced much more, in Puerto Rico, by the younger age groups, where of course the rates are lower. This is a very well known difficulty, and vital statisticians have recourse to what is called *standardization*. This means that in comparing death rates in two populations, an attempt is made to correct for differences in the age distributions by working out what the death rates would have been if the two populations had both had the same age structure.

In this problem, age enters into the picture as a variable which may differ on the average in the two groups which are being considered, and

may distort the comparison which we wish to make. Age is, in fact, a nuisance in this problem. Mr. Atkins (1959) has called factors of this sort " contaminants ", and they are a great source of difficulty in interpreting data.

These difficulties are to be seen at their most exasperating in the interpretation of clinical data. A physician wishes to assess the value of a new treatment for patients with a particular disease. He collects records of clinical response, using the new treatment, and looks around for a control group. He may be tempted to compare each patient's response with his response during some previous treatment on a standard therapy. But can he be sure that these responses are not influenced by environmental or climatic changes during this interval, or by his new-found enthusiasm which may be transmitted to his patients? If he compares the patients with a different group previously treated by another method, how can he be sure that the two groups are similar in all relevant respects? Factors like age, sex, social status, which may affect response can be recorded and compared, but what about the severity of the disease, and indeed a large number of unsuspected factors which might affect the result? To compare results in two groups in different medical centres is to introduce further possibility of bias, particularly through different standards of diagnosis or hospital admittance.

The prospect sounds bleak, but we should remember that the problem is a general one arising in many branches of science. If we wish to compare the effects of different treatments on individuals whose level of response varies randomly (and this covers almost all biological material), how can we ensure any valid comparison? The main point is that however much we try to allow for factors that we feel might influence the comparison, we can never be sure that there are not others which we had not thought of. The solution is to use the device of *randomization*. The groups can be made comparable in various respects thought to be relevant, e.g. the physician could arrange that each group had an equal proportion of males to females; but within these restrictions, treatments should be allocated to individuals at *random*. This means, strictly, by some sort of mechanical randomization device like spinning a roulette wheel or tossing a coin, but in practice there are tables of random numbers from which the allocations can be made.

Now, randomization clearly does not ensure that the groups are very similar in all respects, but it does mean that allocations which are *seriously* unbalanced with respect to any factor, suspected or not, are rather unlikely to occur. In fact we can work out the probability that whatever difference we find between the responses in the two groups could have arisen just by an unfortunate chance allocation. This is the problem of a significance test for differences between groups, an example of which has been discussed above (Table V).

This particular example was taken from a clinical trial done some years ago. One of the interesting points about it is that, like many such trials, it was performed at a number of different centres. It would, in these circumstances, have been quite wrong to arrange that some centres used one treatment while others used the second treatment. The essential point is that subjects must be allocated randomly within each centre; then any differences between the type of patient seen in various centres or the standards of assessment used will not seriously distort the comparison.

In many clinical experiments it is possible to give more than one treatment on the same subject. This is often true of treatments for chronic disease where some short-term alleviation of symptoms is sought. Analgesic and hypnotic drugs, for instance, can usually be given repeatedly on the same subject. In general this sort of experiment is more informative than one in which a subject can receive only one treatment. The reason is that random variability in response from one occasion to another on the same subject will usually be less than random variability from one patient to another. For a given number of observations, therefore, comparisons will usually be more precise if they are made on the same subject than if they are on different subjects, and it will be correspondingly easier to sort out the real effect from the random variation—easier, that is, to get a significant result.

Controlled trials involving random allocation are now so much a feature of clinical research in this country that we are apt to forget that they are almost entirely a post-war development, but that the principle of randomization, and indeed the whole concept of experimental design as a subject to be studied from a statistical point of view, arose in the 1920s. It was introduced in agricultural work by R. A. (now Sir Ronald) Fisher and was an accepted feature in animal experimentation in the 1930s. In biological assay, for example, it is important not only to estimate the potency of a test preparation of, say, vitamin D, but to determine also the precision of this estimate. This precision will depend among other things on the number of animals used in the assay, and on the variability of response in similarly treated animals. All this can be done by making use of the appropriate statistical theory, but the result will not mean very much unless we can be sure that no bias has entered into the allocation of animals to different dose levels. This allocation should, therefore, be random.

As an example of a rather more subtle experimental design, here is a plan used by Squire (1950), investigating the diameters of weals caused by different concentrations of histamine pricked into the skin of the forearm.

		Right arm		*Left arm*	
		Lateral	*Medial*	*Lateral*	*Medial*
Site	2 ins. below elbow	A	B	C	D
		B	A	D	C
		C	D	B	A
	2 ins. above wrist	D	C	A	B

The columns represent the medial and lateral borders of the two forearms, the rows represent four equally spaced sites between the wrist and elbow, and the letters represent four concentrations of histamine.

This design is called a latin square, and you notice that every treatment occurs once in each row, and once in each column. This means that general differences in response from one side to another down the two arms, or from one position to another along the arm, will not bias the comparison of responses for the four doses. We often say that these two factors are eliminated from the variation, and the result is that the random variation is smaller than it would otherwise be. We have explained, and controlled, some of the variation, and this can be taken into account in the statistical analysis.

You may wonder how randomization comes into this experiment. After all, the arrangement of treatments seems highly organized and not at all haphazard. The answer is that there is a large number of possible latin square arrangements of a given size. The arrangement to be used should be chosen at random from all possible arrangements, and the standard book of statistical tables, that by Fisher and Yates, contains instructions on doing this.

Controlled experimentation, then, has a valuable part to play in many branches of medicine, but there are many problems, essentially statistical in character, to which the method cannot be applied. This is generally true of questions concerning the role of certain environmental factors or personal habits or experiences in the aetiology of a particular disease. Several years ago the possibility was put forward that certain immunization procedures carried a risk of subsequent poliomyelitis. It would obviously have been entirely out of the question to allocate children to two groups, to immunize one group and to withhold immunization from the other. Apart from the overriding ethical objection, the numbers needed would have been immense because the risk is quite small. The only way to tackle the problem is by examining the experiences of infants who are immunized, or not immunized in the ordinary course of events, and tread extra-cautiously in interpreting the results.

With this sort of problem there are two main approaches—by *retrospective* and *prospective* surveys. We are trying to see whether factor F affects the chances of getting disease D. In the retrospective method we examine people with and without D, and see whether they differ in the

frequencies with which they exhibit factor F. In the problem I have just mentioned, for instance, two groups were formed, of children with and without poliomyelitis, and the frequencies with which children in these two groups had recently been immunized were compared. Similarly, in the classical investigations of Doll and Hill and others on the relationship of smoking and lung cancer, two groups were formed—of patients with and without lung cancer—and the frequencies with which patients in the two groups reported a history of smoking were compared.

In the prospective method, groups of people differing with respect to factor F are formed, and are then followed up so that the incidence of disease D can be compared in the two groups. The smoking and lung cancer study has also, of course, been done prospectively, both in this country (with doctors as subjects) and in the United States.

Either of these methods is subject to a difficulty of interpretation similar to that discussed at the beginning of this section. If factor F is associated in the population with disease D, how can we be sure that both F and D are not caused by another factor X, in which case it would be quite wrong to say that F causes an increase in D? We can never have the assurance provided by a randomization experiment, but at least we can take all the X's we can think of, like age and sex, and either plan in advance or verify after the event that the groups do not differ in these respects. If they do differ, then this must be allowed for in the calculations. In a prospective smoking study, for instance, the smokers would probably have a different age distribution from the non-smokers, and this would have to be allowed for by standardization, in the way I mentioned earlier. Clearly, any non-randomized study of this type has to be scrutinized very carefully in the light of general experience, and in the light of other types of experimental evidence.

In conclusion, the main point to be emphasized is that statistical studies may in some situations be relatively unimportant, and in others uniquely informative, but that in general they are complementary to, rather than in conflict with, other types of investigation. Many investigations in biology and medicine are statistical to an extent of which the investigators themselves are sometimes unaware. The clinician, in making judgments on the basis of his wide experience is surely using statistical evidence—even though it is not explicitly set down in writing.

I would like to make a final point. The most elaborate statistical treatment will not improve the inherent quality of the original data. It is much better to make good observations with no statistics than to obtain mediocre data with some excellent statistical analyses. In reading papers try to penetrate beneath the veneer of statistical respectability and see whether the author really has anything to say. Lasagna (1955)

has described certain types of authors as "*t*-test terrors" and "chi-square cavaliers". Statistics are perhaps all the better for being treated with a little healthy disrespect.

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PORTRAIT OF THE LATE SIR ARCHIBALD McINDOE

Sketch portrait of the late Sir Archibald McIndoe by Anna Zinkeisen. Painted during the war at East Grinstead. Another painting of Sir Archibald by Miss Zinkeisen is in the War Museum. This was painted whilst he was operating.

CEREMONY OF PRESENTATION OF DIPLOMAS

THE THIRD ANNUAL ceremony of the presentation of diplomas was held on the afternoon of 8th June 1960. The Edward Lumley Hall was filled to capacity with diplomates and their relatives by the time the President and Council, accompanied by representatives of the Court of Patrons and preceded by the Mace, processed up the Hall and took their places on the dais. Also represented were the Court of Examiners and the Boards of each of the Faculties, each person wearing the appropriate robes of the College.

The President (Professor Sir James Paterson Ross, Bt.) opened the proceedings by welcoming the assembled company in the following words:

" This is an extraordinary meeting of the Council in more senses than one. First, because it is not on the ordinary Council Day as it is an extraordinary meeting; secondly, the business always goes through very smoothly on these occasions; and, thirdly, we have, we are very glad to have, and we welcome a large audience to witness this particular extraordinary meeting. We are delighted that you should come here to share in the triumphs of your sons and daughters and friends, because I know quite well that many of you must have shared their anxieties beforehand, and so now it is right that you should share their success also. And it is right that we should have the Court of Examiners here with us because, although I know many candidates cannot accept it, it is true that the examiners are just as anxious for the success of the candidates as anyone else. But all the College would like to congratulate those who have been successful in the examination, because it is astonishing what excitement and emotion there is in this building at the examination times. Not only the parents and friends, but also the staff of the College are just as excited and interested as anyone else. So we welcome you here to this extraordinary meeting. The first item on the agenda is the admission of Professor Carl Semb to the Honorary Fellowship."

Mr. A. Dickson Wright, the Senior Vice-President, then presented Professor Semb to the President and Council, and Sir Clement Price Thomas gave the following citation:

" Mr. President: It affords me great pleasure to present to you my friend Carl Semb, Professor of Surgery in the University of Oslo, Chief Surgeon in Surgical Clinic III in the Ullevål Hospital. Incidentally, just recently a great friend, and I suspect a patient of his, has built and equipped a new clinic and a large research department as a personal tribute to him, a rare mark of distinction for any surgeon.

" Carl was educated at the University of Oslo, of which he is a Doctor of Medicine. Early in his career he came under the influence of the late Professor Bull, and I feel that it was this influence which turned his mind to the problems of thoracic surgery, which for the time at least became his main preoccupation.

" Following in the footsteps of his distinguished predecessor, he soon made his mark in the field of pulmonary tuberculosis; with his friend and medical colleague, Dr. Alexander Tuxen, who was also his patient, he established at the Vardhåsen Sanatorium a tuberculosis service which was equalled by few and became the envy of many. His outstanding contribution to this field was, in my opinion, the devising of the operation of extra-fascial apicolysis, a procedure which ranks in significance with the first introduction of the operation of thoracoplasty. This operation still goes by the name of Semb and even today when resection has become the mode it is still invaluable in certain groups of patients.

" I believe Semb is the only surgeon extant who has had his name attached to an artificially created space, for the space left after the apex has been mobilized is called the Semb space.

" As befits a Professor of Surgery, his interest in his subject is catholic. Indeed, he is at home in all the systems of the body. You will remember, Sir, that not long ago in this very Hall he gave us a fascinating Moynihan Lecture on his very considerable experience with segmental resection of the kidney in the conservative surgery of renal tuberculosis. By his vision in inviting to his clinic from the United States his fellow-countryman, Smith Petersen, he has established a centre for the treatment of painful arthritis.

" It is rumoured that our Honorand of today does sleep for some part of the twenty-four hours, but I am uncertain as to when, for he works till late at night and by 6.45 in the morning he is in his clinic with his team, discussing the patients who are for operation that morning. Those who have been privileged to attend these sessions will have fully appreciated his keen clinical sense and his extremely human approach to these problems. If the visitors are English then the whole proceedings are carried on in that language, the case notes are freely translated and the whole discussion is carried on as naturally as in one's own clinic at home. I suspect that Norwegian is sometimes used, but I have never heard it.

" He has gathered around him a band of keen, intelligent and loyal assistants and very many of the young surgeons practising in Norway stem from Department III at Ullevål. Professor Semb surely fulfils all the prerequisites of a great surgeon: that he shall treat his patients faithfully, that he shall advance the margins of knowledge in the science and art of surgery, and that he shall train a band of young disciples who will carry on the torch of learning which he has lit.

" The warmth of the friendly greeting which he gives to his visitors and the extremely high standard of the work in his clinic has made Ullevål Sykehus a Mecca for all foreign surgeons.

" True to the Viking in him his chief extra-curricular activities are yachting and fishing, and it may have been that it was this love of the sea which formed the first link in his friendship with his benefactor who built his clinic, for I understand that the latter's great interest is in whaling. In the winter time it is but natural that, Norway being the home of the ski, Carl should go skiing.

" During the last war, after the invasion of Norway and for the succeeding three years, Carl became the head and the inspiration of the Resistance movement, and he was responsible for the organization of a great underground army. The risks he took at that time are incalculable, and it was for this work that he had conferred on him the George Medal for bravery.

" The time came, however, when he had to leave his home in order to escape the close attention of the Gestapo, who were taking a great interest in him. This he did at night through the woods, over the border to Sweden. But before he left he had a party of all his friends and they consumed the remains of the contents of his cellar so that they should not fall into enemy hands. While in Sweden, he continued his work of great military importance, but equally significant was his work as an unofficial ambassador for his own country. The value of his services in both these fields cannot be over-estimated.

" He was actively engaged in the Korean war, for which he holds three Service decorations, and since that time he has been largely responsible for the establishment of a civilian hospital, sponsored by the Governments of the three Scandinavian countries. This hospital not only treats the Korean sick, but also trains doctors who in the future will be a solid asset to Korea.

" Carl Semb has been honoured in many countries. He is an Honorary Fellow of the American College of Surgeons, and of the American Association for Thoracic Surgery; a member of many other foreign medical and surgical societies; and in his country he is an Honorary Member of the Thoracic Society and the Society for Thoracic Surgery, and a corresponding member of the Association of Surgeons.

" During the whole of his busy life he has been constantly supported by his charming wife, and we are very glad to have Mrs. Semb with us this afternoon.

" It is for these reasons, Mr. President, that we find in Carl Semb a man of the greatest integrity and of the warm friendliness which touches one's heart, that I have great pleasure in presenting him to you so that he may receive at your hands the Honorary Fellowship of our College."

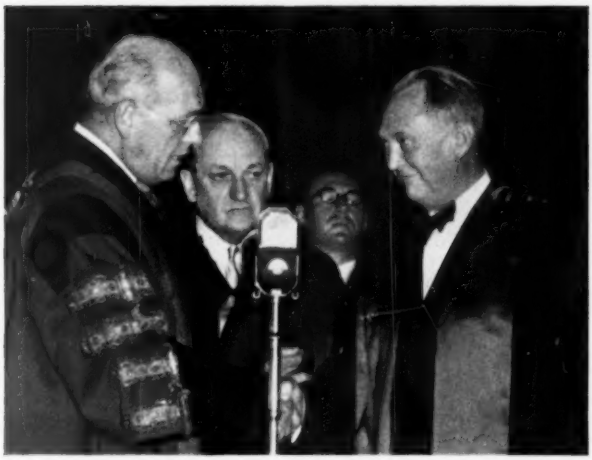

Fig. 1. The President admitting Professor Semb to the Honorary Fellowship. In the background are Mr. A. Dickson Wright (Senior Vice-President) and Sir Russell Brock.

After the President had admitted him to the Honorary Fellowship, Professor Semb spoke thus:

" Mr. President, Members of Council: May I extend to you my sincere thanks for bestowing upon me an Honorary Fellowship of the Royal College of Surgeons of England. I regard it as an extraordinary and overwhelming honour for which I do not feel in any way good enough. But because of this I appreciate it all the more. May I also thank Sir Clement for his nice words to me. I am not sure they are all true, but I appreciate them and certainly run the risk of these words going to my head.

" I am very happy to be invited to this ceremony and to be a Fellow of this Royal College. I know that the Fellows of this Royal College have made great contributions to surgery and will always do so in the future, and I thank you very much for this honour."

The next item on the Agenda was the granting by the Council of diplomas of Fellowship to the candidates successful in the recent Final Examination, on the motion of Mr. A. Dickson Wright, Senior Vice-President and past Chairman of the Court of Examiners.

Members of the Council and others who were to present candidates for the receipt of their diplomas then moved to the back of the Hall to join the parties of diplomates from their own medical and dental schools. Then followed 25 processions, Members of Council and the Court of Examiners presenting the Fellows and Members, and the Fellows and Licentiates in Dental Surgery and Fellows in the Faculty of Anaesthetists being presented by members of the appropriate Board of Faculty.

Fig. 2. Professor Semb addressing the new diplomates.

At the request of the President and Council, Professor Semb then addressed the new diplomates:

" Mr. President, Members of Council: It is a great privilege and pleasure for me to be able to address the new diplomates—the surgeons who have reached the stage of qualifying in surgery.

" You represent the new and younger generation who will take part in the development of surgery—including dental surgery and anaesthesia—in the future. We, your older colleagues, are happy to have you with us. We will always take great interest in your contributions to surgery. We realize, on an occasion like this, the truth of the saying *Ars longa, vita brevis*. The art of surgery is immortal. The surgeon, however, has only a short lifetime in which to make his contributions.

" As an art, surgery demands from the surgeon unceasing effort, great enthusiasm and a humble attitude. In view of this, we would like to thank you for making surgery the aim of your life.

" Surgery can be characterized by the words of Sir Winston Churchill, who is an Honorary Fellow of this College, to the people of England in 1940, when he said: ' I cannot promise you anything but blood, sweat and tears.'

Surgery certainly brings us triumphs, but we shall soon forget these. The defeats, however, we will always remember; they should be kept in our minds and stimulate and encourage us to further progress in surgery.

" Surgery is a duty, not a labour; an art, not a business. It brings us in close contact with the laws of Nature, the laws which direct and dominate our life and health. Our work in surgery gives us an opportunity to get a glimpse of the unfathomable secrets of Nature, the secrets which represent the real truths of life. Surgery teaches us that we can depend fully on these laws and therefore we should make every effort to find the truth. By surgery we learn to admire the masterpiece of Nature represented by the human body, teaching us respect for life and respect for the individual.

" Surgery is a science which develops rapidly. Surgeons in the past, however, have often had a tendency to look upon *their* surgery as the sublime and ultimate of the possibilities. The Surgeon-General of Napoleon, Larey, said 160 years ago: ' Surgery has now come so far that the future can bring us no further progress.'

" Larey characterized by these words the difficulties of surgical technique at that time, without the aid of general anaesthesia, antiseptics, aseptics or even analgesic drugs. Under such conditions he was right.

" But *tempora mutantur*, time changes, and new aids and remedies have come and radically increased the scope and possibilities of surgery. Modern aseptics, the development of anaesthesia, blood-transfusions, antibiotics, development of technique—all these have made it possible to extend surgery to all organs in the human body. This could lead us to the belief that we, the surgeons of to-day, represent the summit of surgical development just as Larey did 160 years ago.

" But the history of surgery teaches us that surgery has only passed through its initial difficulties and that the future will bring us even greater advances. Countless surgical problems are still awaiting their solutions, both with regard to more perfect immediate and late results of our operations, and the opening-up of completely new fields of surgery.

" With advancing knowledge the demand on surgery and on the surgeon is correspondingly increased. The development of surgical technique and of laboratory methods have markedly increased the possibility of a correct diagnosis, but these developments must not allow us to forget the importance of clinical observation of the patient and the personal and human contact between the patient and his doctor. The surgeon should examine the personality and the psychological state of the patient even in cases of simple mechanical surgical procedure.

" Modern surgery has become a weapon of such power that it is possible to carry out mutilating operations without endangering the life of the patients, a real *chirurgia major atque crudelis*. We must therefore avoid misuse of surgery. In the words of my teacher: 'A surgeon is a man who knows how to operate, but also knows when to abstain.'

" Modern surgery requires from the surgeon high morals and high ethics as well as great technical and clinical experience.

" Research will always play an important rôle in the medical profession. The surgeon should at all times keep his mind open for new pathways and should look upon every case as a new and individual problem. Two cases are never exactly alike. The problems from clinical surgery should be solved by experimental and laboratory research based on the methods adopted from the basic sciences of anatomy and physiology, pathology, chemistry and biochemistry, physics and biophysics.

" The clinical observation by the surgeon and the exact methods of the scientist will mutually stimulate and inspire each other to further development of surgery. Work on these lines will bridge the gap between clinical problems and basic research, and this will create safer and more effective surgery.

" If we to-day look upon the map of the world and try to find out where people have easy access to modern surgery, we will find that the number of these people is comparatively small and that they are mainly confined to relatively few centres of the western world. In the greatest part of the world there is a marked shortage of surgeons and surgical services. Many countries totalling a population of over 100 million people have not a single medical school or a single university clinic. In many parts of the world we will find on average only one surgeon for half a million people and very few hospitals. Therefore the majority of the world's population is dependent on less-developed surgery or on no surgery at all. But all people, regardless of location, colour, race, religion, economy, technical development or politics, are in great and urgent need of highly qualified surgery. Therefore the field of surgery is open throughout the world and hundreds of millions of people are eagerly awaiting young surgeons like yourselves to help them.

" The work and life of the individual surgeon will differ according to the various conditions in different places. The surgeons in Africa, for example, will have different problems to solve from those of surgeons in London, but their contributions are equally valuable to humanity. The spread of highly qualified surgery to all people in the world

has the greatest ability to unite all people in the fight for freedom from disease. Surgeons, in their work throughout the world, bring people of all nations together in friendship. In this way surgery can create greater understanding and peace in the world.

" To every one of you I would like to extend the hope that you will bring surgery to increasing perfection and to the aid of all human beings."

The President then asked the Senior Vice-President, Mr. A. Dickson Wright, to move a vote of thanks to Professor Semb for his address, and Mr. Dickson Wright spoke thus:

" Mr. President: It is my privilege to accord to the Speaker a vote of thanks from all assembled here to-day. We will all remember this Viking who came over the seas to wish the 231 people who received their diplomas to-day God-speed in the profession of their choice. You will remember his words and probably read them again in the *Annals* of the College. They are moving and stirring words and with them in your hearts you will go forward to a great future in the professions of your choice.

" He has said that nothing but blood, sweat and tears await you in the profession, and success will only be gained if you avoid producing blood, sweat and tears in your patients.

" Sir Clement Price Thomas has told you somewhat of the great man who has spoken to you. Although he is a Fellow of this College, qualified on the same day as you are, you gather he has done a lot more than you have and therefore was entitled to exhort you in the way he did. He has a wonderful past, especially in those days in the war, those black days when Norway was invaded and we did our best in our feeble way to help them. And through those dark years they put up a show in the Resistance which was not equalled by any other country in the world, and the surgical Scarlet Pimpernel of that Resistance was Professor Carl Semb.

" In these days of space travel it was pointed out that he had created a space himself: actually I believe he has named two spaces because the one that I thought was Semb's space was quite a different one from that which Sir Clement Price Thomas described. So he is the author of two spaces, he has created two vacuums in the human anatomy which is more than any of us ever hoped to do.

" You had a word of exhortation from a very great man to-day, and when the year 2000 comes round some of you will be sitting and saying, ' I remember in 1960 being addressed by Professor Carl Semb when I started on my surgical or dental career '. Therefore it is with very great pleasure, and an honour, that I am able to propose this vote of thanks to our Speaker to-day."

Mr. Peter T. Bruce, a young Australian surgeon who had received his diploma of Fellowship on this occasion, then spoke from the body of the Hall:

" Mr. President, Members of the Council: May I on behalf of all who to-day were presented with one of the diplomas of this College say just a few words. We would like to thank you most sincerely, not only for bestowing on us the great honour of making us Members or Fellows of this wonderful College, but also making possible this unforgettable ceremony.

" Nearly all of us on this side of the Hall recently passed an examination. I have no doubt that my colleagues and I enjoyed every minute of this, and this, Sir, is due entirely to the most pleasant atmosphere created by the Examiners and we would like to express our thanks to them. So from all the corners of the earth, thank you."

The President thanked Mr. Bruce, and closed the meeting; the Council then withdrew in procession.

GRANT OF FELLOWSHIP DIPLOMAS

AT THE RECENT Final Examination for the Fellowship, five candidates out of twenty-two were successful in Ophthalmology, nine candidates out of twenty-one in Otolaryngology, and 120 out of 423 in General Surgery.

At an extraordinary meeting of the Council on 8th June, Diplomas of Fellowship were granted to the following:

JEFFREYS, Thomas Eurig (*Guy's*).
JONES, Rhys Tudor Brackley (*St. Mary's*).
COTHAY, Delia Margaret Helen Hernaman (*Westminster*).
SOMERVELL, James Lionel (*University College*).
INGALL, John Robert Franklin (*Westminster*).
DOLPHIN, Jeffrey Michael (*Birmingham*).
KIRKUP, John Robson (*St. Mary's*).
*KEITH, Cyril Gregory (*King's College*).
WEBSTER, John Herbert Harker (*Westminster*).
ANDERSON, Peter Christie (*Middlesex*).
LAWSON, Lincoln James (*Birmingham*).
ATKINSON, David Worthington (*Guy's*).
SWANN, Malcolm (*Westminster*).
HAWLEY, Peter Robert (*University College*).
NELSON, Martin Andrew (*St. Mary's*).
SMITH, Howard Calvin (*Coll. Med. Evangelists*).
AGARWAL, Ratan Lal (*Lucknow*).
EADIE, John Wallace (*St. Andrews'*).
DAVIES, David Millward (*University of Wales*).
BOYD, Donald MacGregor (*Manitoba*).
COZENS-HARDY, John Nathaniel (*St. Bartholomew's*).
SHEILS, John David (*Sydney*).
BURHAN, Mohomed Nafick (*Ceylon*).
*GRAY, Tom Douglas Huon (*Liverpool*).
†O'REILLY, James Alphonsus (*Dublin*).
ALOYSIUS, Thethravusamy Joseph (*Madras*).
CONSIDINE, John (*Dublin*).
ENSELL, Francis John (*Birmingham*).
MYNHARDT, Michael Rudolph (*Witwatersrand*).
TALWAR, Benarsi Lal (*Bombay*).
*GUPTA, Jagdish Sarup (*Punjab*).
HAYES, Keith Leslie (*Melbourne*).
†JONES, Kenneth Thomas (*Adelaide*).
LYALL, Alexander David (*Aberdeen*).
MULLICK, Rajendra Nath (*Lucknow*).
PETERSEN, Colin Victor (*Queensland*).
†CHANDRASEKHA, Shrof Ramasetty (*Madras*).
FERGUSON, Ian Allan Le Gay (*Melbourne*).
GARNER, Ralph Lindsay (*Sydney*).
GIBSON, John Nevill (*St. Mary's*).
MORRISON, Malcolm Cameron Tatham (*St. Thomas's*).
SAMSI, Suniti Ratnakar (*Bombay*).
SCARLETT, Geoffrey Anthony Gerard (*Sydney*).
BANSAL, Prakash Chandra (*Lucknow*).
BLOWER, Alan Paske (*Guy's*).
BROADHURST, Bernard Wade (*St. Thomas's*).
CALVERT, Denis George (*Middlesex*).
*CULLEN, James Finbarr (*Dublin*).
DHARBHAUMIK, Amal Kanti (*Calcutta*).
LISTER, Ian Stuart (*Middlesex*).
MAZUMDER, Pradip (*Calcutta*).
MENON, Mookkassanairveettil Pullare Achutha (*Madras*).

MOLLOY, Patrick John (*New Zealand*).
SEIN MYINT (*Rangoon*).
SIMKIN, Eric Philip (*Middlesex*).
SOLOMONS, Donald (*Witwatersrand*).
SPRIGGE, Geoffrey Williams (*Westminster*).
UPTON, Ralph Denison (*Sydney*).
*BOWDEN, Bernard James (*New Zealand*).
BRIANT, Ernest Raymond (*Westminster*).
DUNCAN, Graeme Ross (*New Zealand*).
GUNAWARDENE, Muttukuttige Bernard Clement Perera (*Ceylon*).
HANDELSMAN, John Ellis (*Witwatersrand*).
HASSO, Labib Naiem (*Baghdad*).
ISWARIAH, John David (*Madras*).
KENNEDY, David Robert Holden (*Melbourne*).
KITCHIN, Reginald Jack (*Witwatersrand*).
KURUVILA, Jacob Thannikal (*Ceylon*).
LAURENCE, Michael (*St. Mary's*).
MAHALUXMIVALA, Sam Minocher (*Bombay*).
MANGAT, Teja Singh (*University College*).
OMMAYA, Ayub Khan (*Punjab*).
ROXBURGH, Robert Alexander (*St. Bartholomew's*).
SAGAR, Chandramma Dayananda (*Mysore*).
SEDKY, Mohyie El-Din (*Cairo*).
VIEYRA, Harold John Kevin (*Madras*).
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WYNNE-DAVIES, Ruth (*Royal Free*).
ALLMAN, John Gordon (*Sydney*).
BENNETT, Richard Clayton (*Adelaide*).
BURGESS, David Martin (*Charing Cross*).
CHAMBERLAIN, Geoffrey Victor Price (*University College*).
Da ROZA, Anthony Charles William Mosbergen (*Hong Kong*).
DAVIDSON, James Robin Musgrave (*New Zealand*).
DEAN, Alan Charles Barclay (*Aberdeen*).
GAMPEL, Basil (*Cape Town*).
HACKETT, Arthur Henry (*New Zealand*).
HOLLINGS, Raymond Moulton (*Sydney*).
†JOBBINS, Leslie Keith (*Queensland*).
JOHNSON, Henry Ralph (*Melbourne*).
KING, Denis Miles (*New Zealand*).
†KWOK, Frank William (*New Zealand*).
LYNCH, John Brendan (*Queensland*).
†McALARY, Robert Stratton (*Sydney*).
McFARLAND, John Bryan (*Liverpool*).
MEHTA, Bharat Vrajlal (*Bombay*).
PILLAY, Vettivaloo Kandasamy (*Malaya*).
REID, Donald James (*St. Thomas's*).
ROSS, Kevin FitzMaurice (*New Zealand*).
SMAILL, Graeme Ballantyne (*New Zealand*).
VAIDYA, Madho Prashad (*Punjab*).
†WARNER, Ian Henderson (*Melbourne*).
WOO-MING, Michael Ovid (*University College*).
BASNYAT, Soorya Bahadur (*Lucknow*).
BHAVE, Suresh Vishvanath (*Poona*).
CHAN, Cheung-Ping (*Hong Kong*).
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DANGARWALA, Arvind Krishnalal (*Bombay*).
DEV, Arjun (*Rajputana*).
†EDWARDS, William Glyndwr (*King's College*).
EMMETT, Anthony James Jephson (*Queensland*).
HADFIELD, James Irvine Havelock (*St. Thomas's*).
HAMILTON, Ian Michael (*Adelaide*).
LENAGHAN, Leo (*Melbourne*).

McDERMOTT, Francis Thomas (*Melbourne*).
MULLERWORTH, Michael Henry William (*Rangoon*).
REEVES, Brian Francis (*The London*).
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JOHNSON, Ann Elizabeth (*University College*).
LANE, Philip William Bruce (*New Zealand*).
†LEACH, Wilfred (*St. Thomas's*).
MORRIS, John Bentham (*New Zealand*).
PARRY, Eric Leonard (*Sydney*).
SMITH, Philip Henry (*Leeds*).

*In Ophthalmology. †In Otolaryngology.

THE ETHER PAINTING

DR. HENRY R. VIETS, neurologist emeritus to the Massachusetts General Hospital and honorary librarian of the Boston Medical Library, has been a welcome visitor to the College, of which he is an old friend, in recent weeks. He brought with him as a gift for the Library a series of photographs of the original records describing the first surgical operation performed under the influence of ether by John Collins Warren, the anaesthetist being W. T. G. Morton. With these is a view of the Hospital at about that date, a photograph of Morton's inhaler, and a fine coloured reproduction of the "Ether Painting" at the Boston Medical Library. This was painted in Washington, 1882-1893, by Robert Hinckley (1853–1941), a graduate of the Ecole des Beaux Artes and teacher of the portrait class at the Corcoran Art School in Washington. The painting is signed and was presented to the library in 1903.

The picture represents the "Ether Dome" at the Massachusetts General Hospital in Boston as it appeared shortly after 10 a.m. on 16th October 1846. The portraits are painted with great care and show all the individuals present on that date, with a few others added, who were in attendance the next day at the Second Operation. The chief figures are: Gilbert Abbott the patient; J. C. Warren the surgeon; W. T. G. Morton the anaesthetist; Charles F. Heywood the house surgeon; A. A. Gould a senior surgeon with whom Morton lived; Henry Jacob Bigelow son of Jacob Bigelow; George Hayward a junior surgeon; and S. D. Townsend a senior surgeon.

ANATOMICAL MUSEUM

THE SPECIAL DISPLAY for the month of July contains John Hunter's preparations of electric organs in fish.

"OBSERVABLES" AT THE ROYAL COLLEGE OF SURGEONS

46. Moses

USUALLY STANDING ON the mantelpiece in the Inner Hall of the College is a small copy in bronze of the famous statue of Moses by Michelangelo. The height of the figure is 33 cm. and it stands on a base 2 cm. deep (Fig. 1).

Fig. 1.

Born into an ancient but impoverished Florentine family and destined to achieve fame not only as a sculptor but also as a painter, architect and poet, Michelagniolo Buonarroti Simoni, better known as Michelangelo, was born at Caprese in Tuscany in the year 1475. Soon afterwards his parents returned to Florence, where, at the age of thirteen, he was apprenticed to Domenico Ghirlandaio, head of one of the most celebrated workshops of the period. So promising was his work that in the following year Lorenzo de Medici took him into his own house, where he was treated

as a member of the family and was introduced into the "free art school" under the direction of Bertoldo. After Lorenzo's death in 1492 Michelangelo began to feel less confident in his relations with the family and after about a year or so deemed it prudent to remove himself to Bologna,

(Reproduced by kind permission)

Fig. 2.

where he was soon able to support himself by the commissions that his outstanding work gained for him. In 1496 he made his first visit to Rome, where his abilities attracted much notice; but it was not until the spring of

1505, long after he had returned to Florence, that he was commanded by the Pope, Julius II, to prepare designs for his tomb. The plans which were finally approved were elaborate and Michelangelo spent months at Carrara superintending the excavation and shipment of the marble required; but when he returned to Rome he found that the Pope's interest in the project had abated markedly, so, much mortified, he returned to Florence. Two years later, however, he was again called to Rome, to paint the ceiling of the Sistine Chapel, the main theme of the decoration being the story of Genesis from the Creation to the Flood. This undertaking occupied the next four and a half years, at the end of which time he was requested to resume his work on the Pope's monument. Hardly had he done so before Julius II died and his heirs decided that the design should be greatly modified. Originally, the tomb had been planned as a vast free-standing chapel, but in its final and much reduced form it was placed at the end of the transept of St. Pietro-in-Vinculi. Even so, Michelangelo spent the next three years, from 1513 to 1516, in completing three of the main figures, Moses and the Two Slaves, and these are among the most famous of his sculptural works. The two Slaves are now in the Louvre, so the life-size figure of Moses, originally intended for one of the angles of the upper course, to-day forms the main feature of the memorial. The prophet is shown in a sitting position with his head raised and turned to the left, his right arm grasping the tables of the law; and it is supposed that it depicts the occasion of his finding the Israelites worshipping the golden calf, his expression denoting wrath, menace and discouragement. The entire monument was not completed until 1532 and it is supposed that much of the remaining work was carried out by others.

This reduced copy came into the possession of the College in 1943 as part of the Lady Bland-Sutton Bequest. A full-size plaster cast can be seen in the Victoria and Albert Museum (Fig. 2). J. D.

SAYINGS OF THE GREAT

"*The mind inquiring after truth must weigh causes and effects; draw conclusions from reasonable premises, and appeal to principles confirmed by experiment and matter of fact only.*"

Thomas Trotter (1803) *Medicina Nautica*, **3**, 146.

Dr. Thomas Trotter was Physician to the Fleet during the Napoleonic Wars.

(*Submitted by Mr. S. Wood.*)

Contributions are invited.

DONATIONS

During the last few weeks the following donations have been gratefully received:

Appeal Fund—Donations:

£350	Royal Insurance Co., Ltd.
£250	R. Silcock & Sons (further gift)
	Midland Bank, Ltd. (further gift)
£200	Northern Assurance Co. (further gift)
£163 5s. 4d.	Yorkshire Insurance Co., Ltd. (further gift)
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	E. S. & A. Robinson, Ltd. (further gift)
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£52 10s. 0d.	Commander & Mrs. W. Leyland
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	S. Japhet & Co., Ltd. (further gift)
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£26 5s. 0d. p.a.	Savoy Restaurant (Southsea)
£10 p.a. for 7 years + tax	Sir Herbert Butcher
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	K. F. Steven, Esq.
£3 3s. 0d. p.a. for 7 years + tax	D. G. Kennedy, Esq.
£2 2s. 0d. p.a. for 7 years + tax	F. S. Cantwell, Esq.

Voluntary annual subscriptions and donations by Fellows:

The following Fellows of the College, Fellows in Dental Surgery and Fellows in the Faculty of Anaesthetists have generously given donations or have undertaken to make a voluntary annual subscription under Covenant to the College:

W. A. Jackman, T.D., F.R.C.S.
J. H. Johnston, F.R.C.S.
J. G. Matheson, F.F.A.R.C.S.
W. Maxwell Munby, F.R.C.S.
Professor R. S. Pilcher, F.R.C.S.
P. H. Schurr, F.R.C.S.
J. F. Simpson, F.R.C.S.
Brigadier J. M. Weddell, C.B.E., F.R.C.S.

APPOINTMENT OF FELLOWS AND MEMBERS TO CONSULTANT POSTS

D. S. SARDANA, F.R.C.S.	E.N.T. Staff Surgeon to Safdarjang Hospital, New Delhi.
S. R. REYNOLDS, M.R.C.S.	Radiologist to West Herts., and St. Paul's Hospitals.
E. L. TRICKEY, F.R.C.S.	Orthopaedic Surgeon to Edgware General Hospital and Royal National Orthopaedic Hospital.
P. H. SIMMONS, F.F.A.R.C.S.	Anaesthetist to Royal Northern Hospital.
H. R. C. RICHES, M.R.C.S.	Physician in Chest Diseases to Harefield Hospital.
Miss P. M. EDWARDS, F.F.A.R.C.S.	Anaesthetist to Harrow Hospital.
Miss H. M. MAYER, M.R.C.S.	Gynaecologist to Harrow Hospital.
L. R. TWENTYMAN, M.R.C.S.	Homoeopathic Physician to Royal London Homoeopathic Hospital.
H. J. SHAW, F.R.C.S.	E.N.T. Surgeon to Northwood, Pinner and District Hospital.
A. J. HARROLD, F.R.C.S.	Orthopaedic Surgeon to Paddington General Hospital and St. Mary's Hospital.
S. SILBERMANN, F.R.C.S.	E.N.T. Surgeon to Watford Hospitals and Barnet Hospitals.
G. T. F. BRADDOCK, F.R.C.S.	Orthopaedic Surgeon to King Edward Memorial and West Middlesex Hospitals.
G. J. HADFIELD, F.R.C.S.	Consultant General Surgeon to Royal Buckinghamshire and Aylesbury Hospitals.
J. E. CATES, M.R.C.S.	Consultant Physician to United Bristol Hospitals.
D. R. SWEETNAM, F.R.C.S.	Assistant Consultant Orthopaedic Surgeon to Middlesex Hospital.

The Editor is always glad to receive details of new appointments obtained by Fellows and Members, either through the Hospital Boards or direct.

PROCEEDINGS OF THE COUNCIL IN JUNE

AN ORDINARY MEETING OF THE COUNCIL was held on Thursday, 9th June 1960, with Professor Sir James Paterson Ross, Bt., President, in the Chair.

Reference was made to the death of Mr. Edward Lumley, a great benefactor of the College and a member of the Court of Patrons, and the Council stood for a moment in tribute to his memory.

The Lady Cade Medal was presented to Group Captain R. C. Jackson, Member, to whom it had been awarded for his demonstration of the life-saving value to the Royal Air Force of the transportable artificial kidney in the management of patients suffering from acute renal failure, following trauma, blood loss, burns or infection.

Begley Prizes were presented to J. Barrett, G. A. Hunter and R. E. Robinson, all Members, who obtained the highest marks in the last examination in surgery for the Membership.

The following were co-opted to the Council for the year 1960-61, representing various branches of practice:

Ophthalmology	Mr. T. Keith Lyle, C.B.E.
Otolaryngology	Mr. C. Gill-Carey
Gynaecology and Obstetrics	Mr. H. G. E. Arthure
Anaesthetics	Dr. G. S. W. Organe
Dental Surgery	Professor M. A. Rushton
General Practice	Dr. John H. Hunt
Radiology	Professor D. W. Smithers.

The new co-opted member of Council is Mr. Arthure, of Charing Cross and Queen Charlotte's Hospitals. He is a Fellow of this College, and a Fellow and former Honorary Secretary of the Royal College of Obstetricians and Gynaecologists.

The President expressed the thanks of the Council to Mr. Arthur Bell for his services as the co-opted Member of Council representing Gynaecology and Obstetrics during the past five years.

Examiners for the year 1960-61 were elected.

Two Mitchiner Medals were awarded. That for 1959 was granted to Lt.-Colonel I. A. Walsh, M.B., R.A.M.C., for his work in realistic methods of training, with the introduction of procedure training for dealing with mass casualties and the faking of casualties. The medal for 1960 was granted to Major-General W. D. Hughes, C.B.E., M.D., F.R.C.P., for his

services in improving the academic and professional standing of the Army Medical Services, helping the medical officers from the Commonwealth and foreign Medical Services, and introducing research into the teaching of Military Surgery.

Mr. Hedley Atkins was reappointed as the representative of the College on the General Medical Council, and Mr. F. W. Holdsworth was elected to represent the College on the Court of the University of Sheffield.

One diploma of Membership was granted, and one Licence in Dental Surgery.

The following hospitals were recognized under paragraph 23 of the Fellowship Regulations:

Hospitals	Posts Recognized		
	General (6 months unless otherwise stated)	Casualty (all 6 months)	Unspecified (all 6 months)
Warrington — General Hospital (additional)	*Confirmation of temporary recog.* Reg. or S.H.O. 2 H.Ss.		
Leeds—St. James's Hospital (additional)		2 S.H.Os.	
Harrow—Hospital (additional)	2 H.Os.		
Dublin—Our Lady's Hospital for Sick Children		Cas. Reg.	Surg. Reg. S.H.O.
London — Lewisham Hospital (redesignation)			S.H.O. (Orth.) to H.S. (Orth.) (pre-registration)
Barnet — General Hospital	2nd Surg. Reg. 12 m.		

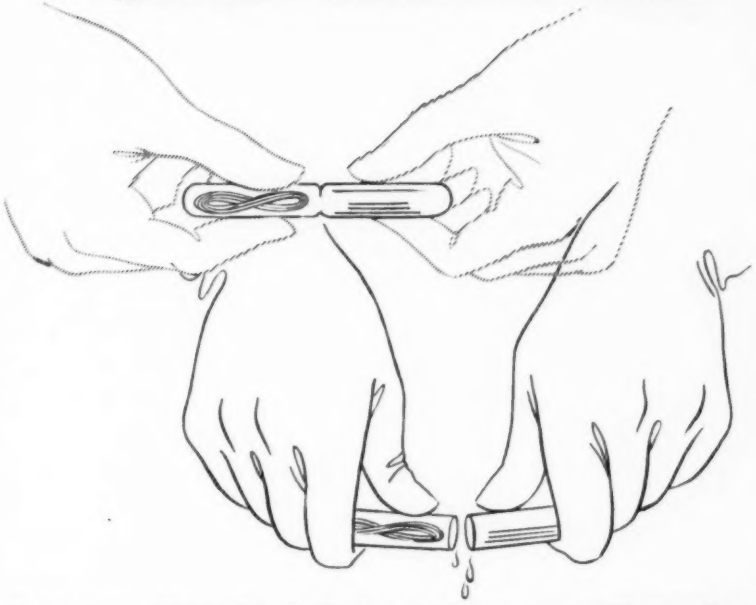
DIARY FOR JULY

Thur.	21		D.Phys. Med. Examination (Part II) begins.
Wed.	27	5.00	Dr. Z. Lowenthal—The history of British-Yugoslav medical relations.
Thurs.	28	2.00	Ordinary Council.
		5.00	Prof. E. E. Dunlop, o.b.e.—Cecil Joll Lecture—Carcinoma of the oesophagus.
Fri.	29		Basic Sciences Lectures and Demonstrations for Dental Students end.
Sat.	30		College closed.

DIARY FOR AUGUST

Mon.	1		College closed.
Tues.	2		Museum and Library closed this month.
Thurs.	4	11.00	Election to Council.
Mon.	22		Clinical Surgery Course begins.

QUICKLY READY TO HAND



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2. Hæmatinic Factors. Of all the factors required for blood formation, only three are likely to be limited in the diet – iron, vitamin B_{12} and folic acid. One cup of Bovril will supply 35% of the adult's daily requirement of vitamin B_{12} (cyanocobalamin) and 20% of the folic acid.

3. Gastric Secretion. The unique mixture that is Bovril is the most powerful known stimulant of gastric secretion – even more powerful than meat extract itself. It is, therefore, particularly useful for elderly patients and convalescents.

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Again the author has used the method of classifying the abnormalities shown on the X-ray and then linking a provisional or even final diagnosis with the clinical findings. In this way the study of the lesion on the film may indicate the proper laboratory investigations to be performed and reduce the list of possible diagnoses to manageable proportions. Essentially for the radiologist, this book will also be welcomed by orthopaedic surgeons, doctors and by students who may be learning to interpret the appearances on bone X-rays.

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1 Rutter, A. G., *Lancet*, 1959, **i**, 1173.
2 Rudd, T. N., *Practitioner*, 1959, **182**, 728.
3 Clark, A. N. G., *Brit. med. J.*, 1957, **2**, 866.
4 Jeffcoate, T. N. A., *Nursing Mirror*, 1958, (Feb) **21**, 15.
5 Ganz, P., and Zindler, S., *Medizinische* No., 1955, **39-30**, 1042.

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